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ACADEMICIAN NIKOLAI DMITREVICH ZELINSKY

(On His Ninetieth Birthday)

Yu. K. Yuriev and R. Ya. Levina

On February 6, 1951, Soviet science and public opinion will commemorate the ninetieth birthday of a remarkable scientist of our country, who enjoys world-wide recognition and has trained several generations of chemists - the Academician Nikolai Dmitrevich Zelinsky, Hero of Socialist Labor, Honored Worker in Science, three times a Stalin Prize winner, and the senior professor of Moscow State University.

Nikolai Dmitrevich Zelinsky was born on February 6, 1861 in the city of Tiraspol, Kherson Province. He received his primary schooling at the county school in Tiraspol, his secondary schooling in the Odessa gymnasium, and his university education at the Novorossisk University in Odessa. Zelinsky was graduated from the natural history section of the university's faculty of Physics and Mathematics and was sent abroad to continue his studies, first at Leipzig and then at Goettingen. In the Goettingen laboratories Zelinsky worked on the synthesis of thiophane. Converting ethylene dichlorohydrin into dihydroxydiethyl sulfide, and the latter into dichlorodiethyl sulfide, Zelinsky had to close the thiophane ring by detaching two halogen atoms from the latter. The intermediate product dichlorodiethyl sulfide unexpectedly proved to be an extremely poisonous substance, however, which later came to be called yperite; Zelinsky was burned very seriously and spent several months in a hospital. Thus, N.D Zelinsky was the first chemist to synthesize mustard gas and the first one to suffer from its effects.

In 1888 N.D.Zelinsky passed his examinations for his master's degree and was appointed a lecturer at the Novorossisk University. He defended two dissertations in the course of the next three years: his master's thesis in 1889, dealing with the chemistry of thiophene· "The Problem of Isomerism in the Thiophene Series"*; and his doctoral dissertation in 1891: "Research on the Phenomena of Stereoisomerism in Saturated Carbon Compounds."** In 1891, Zelinsky was a member of the expedition investigating the waters of the Black Sea and proved the bacterial origin of the

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* N.D.Zelinsky, Selected Works I, USSR Acad. Sci. Press (1941), pp 94-142.

** N. D. Zelinsky, Selected Works I, 145-244. USSR Acd. Sci. Press (1941).

hydrogen sulfide found in the depths of the Black Sea.

In 1893 N.D.Zelinsky was appointed adjunct professor of the University of Moscow. This year marks the beginning of Zelinsky's brilliant career as an organizer, a teacher, and a scientist - at Moscow University, where he is still on the faculty. In Moscow Zelinsky took charge of the analytical division of the laboratory of chemistry and of half of the organic division (the other half being under the direction of Prof. V.V.Markovnikov during the latter's lifetime, i.e., until 1904). In Moscow University Zelinsky took over the basic lecture course on organic chemistry, and the supervision of the students's diploma theses and the scientific research of his associates. For a few years (1899-1901) Zelinsky also delivered the lecture course on organic chemistry for the students of the faculty of medicine. Zelinsky's lectures on organic chemistry were always simple and understandable, richly illustrated with a tremendous collection of preparations and by many interesting and diversified experiments, which were performed in the lecture hall without a single failure by his best assistants: N A.Shilov and others. In our student days we were struck by the extraordinary skill with which Zelinsky selected for the basic course those components of the vast material of organic chemistry that were exceptionally simple in their relationship and logically entered the students's minds. Zelinsky's lecture course on organic chemistry always covered less ground than the textbook, but, by freeing his lectures from unnecessary detail and handling individual topics, with scientific profundity, Zelinsky outlined to his audience the unbroken chain of conversions of carbon compounds with amazing clarity and coherence.

Retaining overall supervision of the laboratory exercises, N.D.Zelinsky assigned direct contact with the students to his associates - assistants and instructors. But he took personal charge of the theses of the individual students and the researches of the fellows, being carried away himself and carrying his students with him. This is what S.S.Nametkin wrote about this academician in 1934: "The student body always valued especially highly the theses that had been done under Nikolai Dmitrevich's personal supervision. The abundance of his ideas, his extremely close, day-by-day, attentive attitude to the slightest details of the thesis, his personal participation at the most critical moments of the research, his constant assistance to the young chemist, not merely in words, but (what was particularly valuable) during the work itself, at the laboratory desk, and lastly, the personal charm of the professor, who was always calm and objective even when occasional (and sometimes very offensive) failures occurred, somewhat cold upon first acquantance, but at bottom extremely sympathetic and kind, fascinated by the experiment no less (if not more) than the laboratory student himself - these have been the fundamental reasons why an enormous number of students and associates have always flocked to Nikolai Dmitrevich....Zelinsky's industry is astonishing, and not solely because of his age. If you pass through Belinsky street late at night even now you often see lights in the window of his laboratory at 11 or 12 pm. In the old days there were no holidays for Nikolai Zelinsky or for his laboratory students."*

Moscow University's old laboratory of organic chemistry, built in 1885-1887 by Prof. V.V.Markovnikov, was not large enough by the beginning of the nineties to hold all the students and associates who wanted to work with Prof. N.D.Zelinsky. Candidates for the diploma, who spent the whole day in the laboratory, had to work in a low and damp cellar. "Our scientific life was spent profitably and in friendly fashion in the cellar, to be sure, under the close supervision and with the direct participation of the young professor, who was fascinated by the work and who was able to impart this fascination to others; we worked without thinking of

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*S. S. Nametkin, Sci. Pap. Moscow State Univ. 3,17 (1934).

the time, weekdays and holidays, often enough with well-proportioned choral singing, for which the professor once received a "reprimand and warning" from the Ministry of Education."* Only in 1902-1905 was Zelinsky able to expand his laboratory with a new annex, which even today houses the student and scientific laboratories of organic chemistry; working in these laboratories afforded many happy days to the pupils of Nikolai Dmitrevich, who were working alongside him, including the writers of these lines.

Alongside his intensive labors in the university, Zelinsky spent considerable time on social and organizational work and teaching outside the university. Thus, in the nineties, Zelinsky organized a chair of organic chemistry in the Moscow Courses of Higher Education for Women, and in the first decade of the twentieth century he organized the Central Laboratory of the Ministry of Finances in Moscow, (which later became the basis for the Institute of Pure Chemical Reagents). He also took an active part in organizing the Shanyavsky People's University, etc.

Zelinsky's scientific, teaching, and social activity in Moscow continued fruitfully for 18 years, down to 1911, when the entire administration of Moscow University was dismissed by order of the Ministry of Education. In token of protest, more than 100 professors and instructors - including Prof. N.D.Zelinsky - resigned. Transferring to St. Petersburg, Zelinsky took the post of director of the modest Central Laboratory of the Ministry of Finances, besides occupying the chair of staple commodities at the Polytechnic Institute.

Only in 1917, after the revolution, was Zelinsky able to return to Moscow University, where he resumed his teaching and pedagogic career with enthusiasm and energy, combining them, after 1934, with his work in the Institute of Organic Chemistry of the USSR Academy of Sciences. At the present time Nikolai Dmitrevich Zelinsky holds the chair of the chemistry of petroleum in the faculty of chemistry of Moscow State University (MSU), is in charge of a section of the Institute of Organic Chemistry of the Academy of Sciences, and is the president of the Moscow Society of Naturalists. The Party and the government of the USSR have thought highly of Nikolai Dmitrevich's activity. In 1926 he was awarded the rank of Honored Worker in Science, and in 1929 he was elected a member of the Academy of Sciences. In 1934 Soviet chemists celebrated the fiftieth anniversary of the scientific and teaching career of Academician N.D.Zelinsky. On this occasion he received a high scientific award from the Committee on Chemical Development: the V.I.Lenin Prize, while the People's Commissariat of Education named the Moscow State University's laboratory of organic chemistry in his honor.

In 1940, during the celebration of the 185th anniversary of Moscow State University, Academician N.D.Zelinsky was awarded the highest honor of the USSR - the Order of Lenin - for his outstanding achievements in the field of chemistry and in consolidating the defensive power of our country, as well as in the preparation and training of scientific personnel. In 1941, Nikolai Dmitrevich was awarded the Order of the Red Banner of Labor on his 80th birthday, for his notable contributions to the solution of scientific problems in organic chemistry; in 1943 he was awarded a second Order of the Red Banner of Labor in connection with the award of decorations to leaders of the petroleum industry. In 1945, on the occasion of the 220th anniversary of the Academy of Sciences of the USSR, the title of Hero of Socialist Labor, with the Order of Lenin and the "Hammer and Sickle" gold medal, was conferred upon Zelinsky for his outstanding scientific achievements in organic chemistry and for his notable services in the training of highly qualified chemists. In 1946, on his 85th birthday, he was awarded a third Order of Lenin for his eminent service to organic chemistry.

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*S. S. Namtkin, Sci. Papers Moscow State Univ. 3,10, (1934)

Academician N.D.Zelinsky is a three-time winner of the Stalin Prize. In 1942, he was awarded a Stalin Prize, First Class, for outstanding scientific research in organic chemistry; in 1946, he was awarded a Stalin Prize, Second Class, (together with Prof. N.I.Shuikin and S.S.Novikov, candidate of chemical sciences); and in 1948, he was awarded a Stalin Prize, First Class, (together with Prof. N.I.Gavrilov) for outstanding scientific research on the chemistry of the proteins.

N.D.Zelinsky published his first scientific paper, "On the Addition Products of Methylamine and β-Methylglycidic Acid," in the Journal of the Russian Chemical Society in 1884, while still a student at the university of Odessa, [1]. During the next 67 years he published over 500 papers, dealing with various problems of organic chemistry and distinguished by their high theoretical and practical interest.

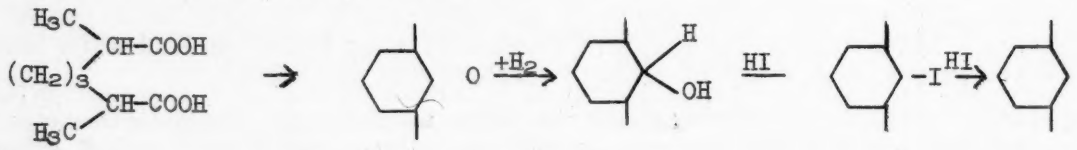
The major lines of Zelinsky's researches have been: the chemistry of petroleum and hydrocarbons, contact transformations of the hydrocarbons, the chemistry of rubber, contact transformations of heterocyclic systems, and the chemistry of the amino acids and proteins, not to mention other fields in organic, inorganic, and analytical chemistry.

The present article is merely a brief, and far from complete survey of the major lines of research pursued by N.D.Zelinsky, which have been further developed by his pupils.

Synthesis of Hydrocarbons

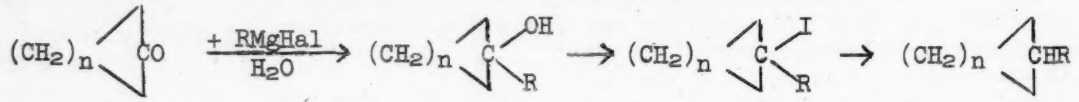
The synthesis of hydrocarbons - cyclic, bicyclic, and aliphatic - has always attracted Zelinsky's attention. These syntheses have shed light upon the chemical nature of many hydrocarbons entering into the composition of petroleum, established the structure and properties of hydrocarbons that had been unknown to chemists before that time, and resolved many theoretical problems in the chemistry of cyclic compounds. Zelinsky has suggested many new methods for the synthesis of hydrocarbons, and many hydrocarbons have been synthesized by him for the first time.

In 1895, N.D.Zelinsky produced the first synthetic naphthene (1,3-dimethylcyclohexane [2]) by converting dimethylpimelic acid into a cyclic ketone, which then yielded the 1,3-dimethylcyclohexane:

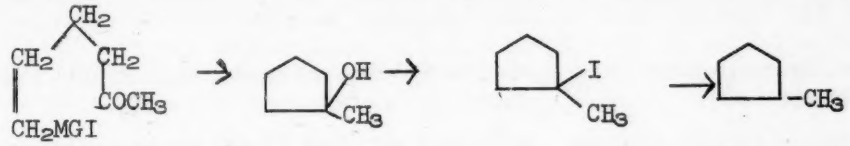


This synthetic naphthene served as a standard for comparison with the so-called "octonaphthene" recovered from a fraction of Caucasian petroleum. Other cyclohexane and cyclopentane hydrocarbons [3-7] were synthesized and described by Zelinsky by the same method, from the respective dibasic acids.

Zelinsky made considerable use of organometallic compounds in his syntheses of hydrocarbons. Thus, he employed organozinc compounds to synthesize 1,2-dimethylcyclohexane [8] and 1-methyl-3-ethylcyclohexane [9]. The reaction of organomagnesium compounds with penta-, hexa-, and heptamethylene cyclic ketones served as the first stage for his synthesis of many new cyclic hydrocarbons [10-19]:



In 1902, N.D.Zelinsky developed an original and exquisite method of cyclizing compounds with open chains of carbon atoms: reacting magnesium with acetobutyl iodide yielded methylcyclopentanol, and the latter in turn yielded methylcyclopentane [20]:

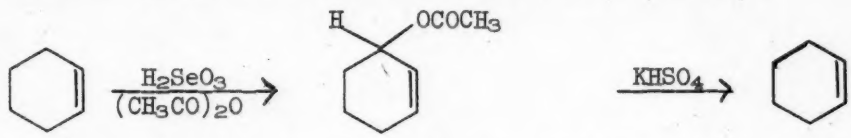


Many unsaturated cyclic hydrocarbons - five membered and six-membered - were first synthesized by N.D.Zelinsky by dehydrating cyclic alcohols with oxalic acid [21-27]. It should be noted that the dehydration of alcohols by anhydrous or aqueous oxalic acid, which has found such wide-spread application, was first described by N.D.Zelinsky [24]. Some of the cycloalkenes thus synthesized were converted into the respective cyclopentane and cyclohexane hydrocarbons, not previously described in the literature, by hydrogenation [21-23].

N.D.Zelinsky synthesized an extremely interesting cyclohexane (though not hydroaromatic) hydrocarbon - 1,1-dimethylcyclohexane - in various ways [28-30]. N.D. Zelinsky and M.V.Gaverdovskaya discovered a singular reaction for reducing alcohols to hydrocarbons: passing the alcohols over activated charcoal at 300° causes the carbon to burn, combining with the oxygen in the organic molecule [31]:

$$R_3COH \xrightarrow[300°]{+\ C} R_3CH + CO_2.$$

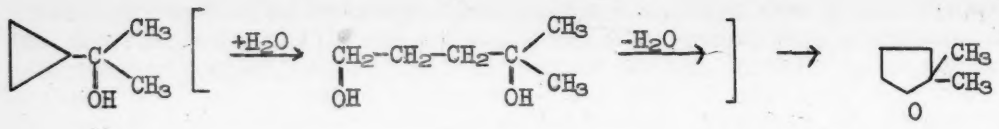
In 1901 Zelinsky was the first to demonstrate that like the bromides and the iodides, chlorides form reactive organomagnesium compounds [32], and he often employed chlorides to synthesize hydrocarbons and their derivatives (alcohols, acids, aldehydes, etc.) [33]. Zelinsky synthesized cyclohexadiene and many of its hitherto unknown homologs [34-37] by various methods; for example:



The synthesis of cyclopentadiene, usually produced by depolymerizing its dimer, was first described by Zelinsky [38]:

Besides the more accessible five-membered and six-membered monocyclic hydrocarbons, monocyclic hydrocarbons that were but little known up to that time were also synthesized in Zelinsky's laboratory: derivatives of cyclobutane and cyclopropane, as well as of cycloheptane, cyclooctane, cyclononane, and the like.

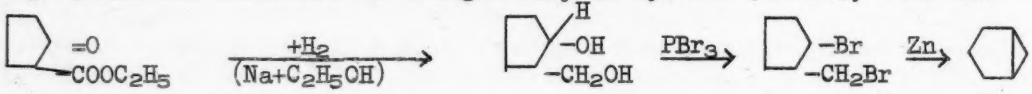
He secured cyclopropane hydrocarbons by synthesizing 1,3-dibromides, which were then reacted with zinc dust (Gustavson reaction). 1,1,2-trimethylcyclopropane, 1,2,3-trimethylcyclopropane [39], and 1,2-dimethylcyclopropane [40] were produced in this manner. During an endeavor to produce a cyclopropane hydrocarbon with an unsaturated side chain by detaching water from dimethylcyclopropylcarbinol, Zelinsky was the first to observe a new and interesting type of isomerization, involving the rupturing of the three membered ring and the formation of a five-membered heterocyclic system that contains oxygen [41]:



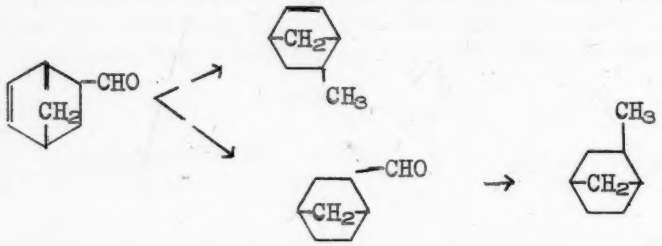
Among the cyclobutane derivatives, Zelinsky synthesized ethylcyclobutane [42] and propylcyclobutane [43].

In the higher cyclic systems, Zelinsky was the first to describe cyclononane [44]. He secured cyclononane and cyclooctane [45] by ketonizing the respective dibasic acids and converting the resulting ketones into hydrocarbons. Among the cyclanes with a large number of carbon atoms, Zelinsky described cycloeicosane ($C_{20}H_{40}$)[46] and cyclotessaracontane ($C_{40}H_{80}$).

N.D.Zelinsky devoted considerable time to the synthesis of rather inaccessible systems of complex and peculiar structure, namely: the bicyclic hydrocarbons - "bridged" and spiran. The class of bicyclic compounds in which two nonadjacent carbon atoms are connected together by a bridge, includes, as we know, some of the terpenes and their derivatives: camphane, thujane, and similar compounds. Many of Zelinsky's papers are devoted to researches in the terpenes, dealing mainly with their contact conversions; but he also investigated the synthesis of terpene hydrocarbons [47] and the structure of bridged bicyclo systems [48-51], such as:

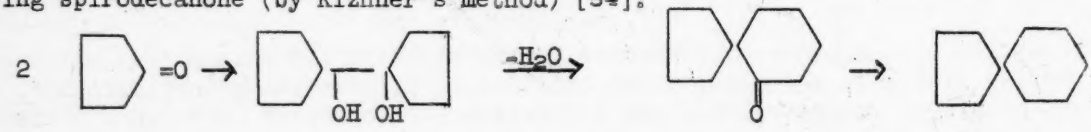


He also described new bicyclic hydrocarbons of the endomethylenecyclohexane series [52]:



The extensive researches of a pupil of Zelinsky, S.S.Nametkin, and his school constitute a development of Nikolai Dmitrevich's researches in the chemistry of the terpenes.*

The researches on the spirocyclanes - bicyclo systems in which both rings have one carbon atom in common - were begun in N.D.Zelinsky's laboratory as far back as 1909 with an attempt to synthesize the simplest spirocyclane [53] (the so-called "Gustavson hydrocarbon". In 1929, N.D.Zelinsky synthesized spiro-(4,5)-decane by reducing spirodecanone (by Kizhner's method) [54]:

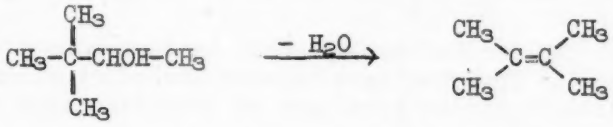


Recently, Zelinsky (together with N.V.Elagina) returned to the synthesis of the spirocyclanes, synthesizing spiro-(4,4)-nonane and investigating its contact conversions [55]. Synthesis of the spiro compounds and study of their chemical and

* S. S. Nametkin, Selected Works. USSR Acad Sci. Press, Moscow (1949).

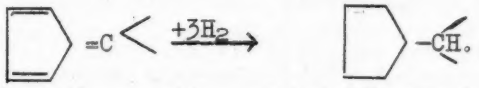
physical properties and of their contact transformations [55] will no doubt shed a bright light upon this topic, which has been the subject of hardly any study up to now.

Zelinsky employed the cleavage of hydrogen iodide from iodides, the pyrolysis of palmitates [56], and the dehydration of alcohols by oxalic acid [24] in his syntheses of alicyclic hydrocarbons; he showed that the dehydration of pinacolyl alcohol by oxalic acid involved a retropinacolic rearrangement:

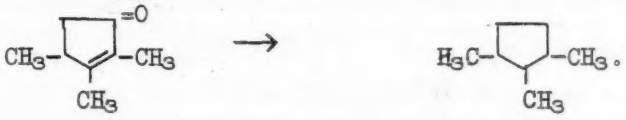


The various methods employed in Zelinsky's laboratory and the synthesis of the same hydrocarbon by various methods enabled him to assign a certain structure to the synthesized hydrocarbon with complete confidence. This brief survey of the results of part of Zelinsky's work in the synthesis of hydrocarbons is enough to demonstrate the wide range of his researches in this field, in every branch of which he had something of import to say.

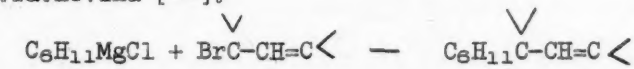
N.D.Zelinsky's research on hydrocarbon synthesis was continued by his pupils, who have described a large number of new hydrocarbons and have developed new methods for their preparation. B.A.Kazansky, for instance, evolved a new method for synthesizing several new cyclopentane hydrocarbons - by hydrogenating the fulvenes [57]:



B.A.Kazansky employed the hydrogenation of trimethylcyclopentenone to synthesize three hitherto unknown isomeric 1,2,3-trimethylcyclopentanones [58]:



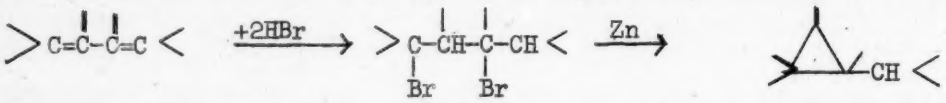
Ya.I.Denisenko also synthesized new cyclopentane and cyclopentene hydrocarbons [59]. A.F.Plate produced several new cyclopentane hydrocarbons with saturated and unsaturated side chains, including 1-methyl-2-ethylcyclopentane [60]. R.Ya. Levina resorted to the pyrolysis of acetates [61] to synthesize cyclohexane and cyclopentane hydrocarbons with methylene and vinyl side chains, while A.F.Plate [62] used this method to synthesize vinylcyclopentane. New cyclohexane hydrocarbons with unsaturated side chains, especially those containing a quaternary carbon atom, were synthesized by R.Ya.Levina [63]:



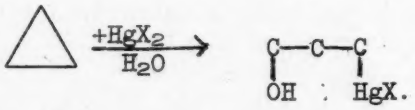
R.Ya. Levina likewise synthesized previously unknown stereoisomeric (cis and trans) β-alkyl decalins, β-alkenyl decalins, β-alkynyl decalins, didecalins, and didecalylethanes [64]. S.I.Khromov described a number of new naphthalene hydrocarbons with straight and branched side chains, as well as with cyclic radicals, in the α-position [65]. B.A.Kazansky and A.F.Plate synthesized a homolog of endoethylenecyclohexane [66].

N.D.Zelinsky's research on the synthesis of the cyclobutane hydrocarbons was

continued by B.A.Kazansky, who greatly improved the method used for their synthesis and secured many new hydrocarbons of this series: alkyl cyclobutanes, stereoisomeric 1,3-dialkyl cyclobutanes, dicyclobutylmethane, and di-(3-methylcyclobutyl)-methane [67]. In the hydrocarbons with three-membered rings, R.Ya.Levina developed a method for synthesizing cyclopropane hydrocarbons from conjugated diene hydrocarbons:



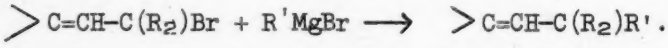
and secured several hitherto undescribed cyclopropane hydrocarbons [68]. R.Ya. Levina discovered a new reaction for opening a three-membered ring, namely: the action of an aqueous or alcoholic solution of a salt of mercuric oxide upon a homolog of cyclopropane [69]:



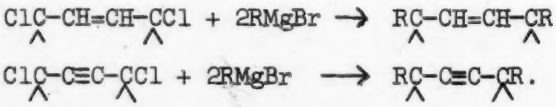
M.I.Ushakov described the synthesis of a derivative of cyclopropane by reacting dianisalacetone with hydrazine hydrate [70], while N.I.Shuikin used the Kizhner reaction to synthesize the previously unknown 2-furylcyclopropane [71].

The synthesis of acyclic hydrocarbons is likewise described in many papers by Zelinsky's pupils. B.A.Kazansky, for instance, synthesized many paraffin hydrocarbons (such as all the hexanes, heptanes, and octanes) and studied their Raman spectra [72], which proved to be valuable source material for research into the composition of gasolines. B.A.Kazansky also described the synthesis and the physical properties of several 1-alkenes [73].

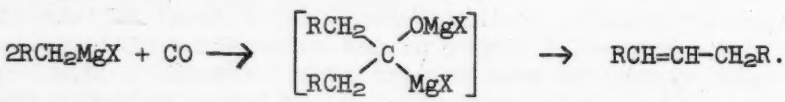
The pyrolysis of acetates was employed in the synthesis of several alkenes: octene-1 [73]; 2,2-dimethylhexene-3 [74]; nonene-1 [75], and heptene-3 [76]. R.Ya. Levina evolved a method for the synthesis of alkenes (and from them the alkanes) with a quaternary carbon atom and synthesized many new hydrocarbons of this type [77]:



R.Ya.Levina employed the reaction of unsaturated ketones (mesityl oxide and "homomesitones" [methylheptenones]) with organomagnesium compounds [78] to synthesize alkanes of iso structure; she also described a new method of synthesizing trans-alkenes and alkynes of normal and branched structure with a centrally located multiple bond [79]:



V.V.Longinov and E.I.Margolis effected the synthesis of a new, difficult tetrahydroterpene: 2,6-dimethyloctene-7 [80]. Ya.T.Eidus, N.V.Elagina, and N.D.Zelinsky described the synthesis of several difficult alkenes by reacting carbon monoxide with organomagnesium compounds [81]:



Ya.T.Eidus and N.D.Zelinsky discovered new reactions: the hydrocondensation of carbon monoxide with the olefins [82] and the hydropolymerization of the olefins

when acted upon by small quantities of carbon monoxide [82].

This far from exhaustive review of the work of N.D.Zelinsky's pupils on the synthesis of hydrocarbons and the study of their properties indicates the development of this field of Zelinsky's research in the work of his school.

Contact Conversions of Hydrocarbons and Heterocyclic Compounds

The researches of N D.Zelinsky on the contact conversions of hydrocarbons are rightly considered classics. Zelinsky discovered and broadly investigated the catalytic dehydrogenation of cyclohexane hydrocarbons, the irreversible catalysis of cyclohexene and cyclohexadiene hydrocarbons, the isomerization of cycloparaffins with five-membered rings into those with six-membered rings, and the hydrogenolysis of cyclopentane hydrocarbons. He was the first to employ platinum, palladium, osmium, and other catalysts successfully in catalytic hydrogenation (in the vapor phase); he made an extensive investigation of the processes involved in the isomerization of carbocyclic systems, etc.

In his 1936 lecture [83], Zelinsky grouped all these contact processes together under a phrase that pithily described them: "contact phenomena that change the chemical nature of hydrocarbons." He added: "Hydrogenation, dehydrogenation, and irreversible catalysis of six-membered ring systems must be regarded mainly from the standpoint of the effect of contact upon the course of chemical transformation. As D.I.Mendeleev saw it, the mechanism of catalysis does not require the formation of intermediate products, but depends upon the degree of strain in the chemical system that is required for the chemical action, which is acquired at ordinary, or slightly increased, temperatures when contact is had with another substance. There can be no doubt of the changes in the dynamic properties of molecules, nor of changes in their forms, during catalysis, and, hence, it is precisely these that are the main cause of the origin and trend of catalytic reactions."

In his search for a catalyst that would effect the dehydrogenation of cyclanes with six-membered rings at temperatures not exceeding 300-310°, i.e., under conditions that eliminate pyrolysis, N.D.Zelinsky discovered that at 300° platinum and palladium black dehydrogenate cyclohexane completely to benzene; at 110°, on the other hand, the same catalysts hydrogenate benzene to cyclohexane [84]:

$$C_6H_{12} \underset{110^\circ}{\overset{300^\circ}{\rightleftarrows}} C_6H_6.$$

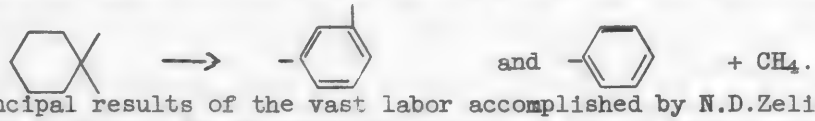
Zelinsky subsequently employed platinum or palladium deposited upon asbestos [85] or activated charcoal [86], these catalysts proving to be particularly stable and active. In his study of catalytic dehydrogenation he found that alicyclic cyclopentane [84] and cycloheptane [87] hydrocarbons are not dehydrogenated; nor can cyclooctane [45] be dehydrogenated normally.

Zelinsky discovered that a nickel catalyst on an aluminum oxide carrier [88] does not break down hexamethylene at all during dehydrogenation, whereas pure nickel decomposed hexamethylene almost completely in Sabatier's experiments, which cast coubt upon the feasibility of catalytically dehydrogenating six-membered rings. Zelinsky's catalyst - nickel upon aluminum oxide - was studied in detail by his pupil, A.M.Rubinshtein [89]. The differing behavior of hexamethylene and other cycloparaffins (with varying numbers of carbon atoms in the ring) in catalytic dehydrogenation enabled Zelinsky to call this reaction "selective catalysis". He made a comprehensive study of catalytic dehydrogenation, covering a large number of individual cyclic hydrocarbons, both qualitatively and quantitatively [90]. In every instance the cyclohexane hydrocarbons lose 6 atoms of hydrogen and are converted into benzenes. It is worthy of note that cyclohexane, in contact with

nickel on aluminum oxide at 300-350°, is converted into toluene, xylene, and dimethylcyclohexane, as shown by N.D.Zelinsky and N.I.Shuikin, the formation of these latter being attributed to the participation of free radicals in this process [91].

The dehydrogenation of some two-ring hydrocarbons - dicyclohexylmethane and dicyclohexylethane - involves the closure of a new ring and the formation of condensed systems [92]:

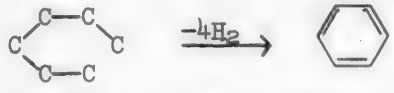
Not all six-membered ring systems proved capable of catalytic dehydrogenation. Endo-methylenecyclohexane hydrocarbons are not dehydrogenated [93], since they are essentially condensed systems of two five-membered rings [94]. 1,1-Dimethylcyclohexane, which is not a hexahydro aromatic hydrocarbon, is not dehydrogenated [95]; the partial aromatization of 1,1-dimethylcyclohexane apparently takes place only after methane has been detached or one methyl group has been transposed [96]:



The principal results of the vast labor accomplished by N.D.Zelinsky and his pupils on the catalytic dehydrogenation of various cyclic hydrocarbons and their derivatives are listed in the subjoined table.

N.D.Zelinsky's catalytic dehydrogenation is today a most important method for investigating the nature of hydrocarbons, both as individual compounds and as constituents of the gasoline and kerosene fractions of petroleum.

Closely related to the catalytic dehydrogenation of six-membered rings is the contact aromatization of paraffin hydrocarbons. As far back as 1931, during an investigation of the catalytic dehydrogenation of gasoline fractions, N.D.Zelinsky and N.I.Shuikin [111] noticed the formation of a largerquantity of aromatic hydrocarbons than should have been recovered from the hexamethylenes and conjectured that it was not only the hexamethylenes, but other classes of hydrocarbons as well that acted as sources for these aromatic hydrocarbons.* And in 1936, B.A. Kazansky and A.F.Plate [113](and, independently of them, B.L.Moldavsky and G.D. Kamusher [114]) discovered a fundamentally new reaction of great scientific and practical importance: the contact aromatization of paraffin hydrocarbons:



The aromatization of many paraffin hydrocarbons, under different conditions and over various contact agents (metals and metal oxides), as well as the mechanism of this complicated reaction, has been studied in detail by B.A.Kazansky, A.F.Plate, A.L.Liberman, S.R.Sergienko, and others [115]; N.D.Zelinsky took an active part in many of these researches [116].

It was in Zelinsky's laboratory that the direct transition from the most inert hydrocarbons, the paraffins, to the reactive aromatic hydrocarbons was effected; up to that time, it had been considered that such a conversion was impossible in principle.

In 1911 Zelinsky discovered the remarkable contact conversion of methyl tetrahydroterephthalate with palladium black; at room temperature this ester was transformed into a mixture of the methyl esters of terephthalic and cis-hexahydrotere-

*The formation of aromatic hydrocarbons during catalytic cracking of hexane had also been observed in 1934 by P.P. Borisov and M. V. Gaverdovskaya [112].

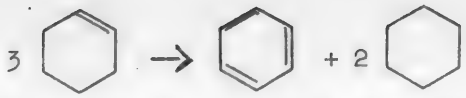
No.	Hydrocarbons and their derivatives subjected to catalytic dehydrogenation	Catalysis products	References
1,2	Cyclohexane; methylcyclohexane	Benzene; toluene	[84,88]
3-6	ortho-, meta- and para-Dimethylcyclohexanes; menthane	Xylenes; cymene	[87]
7-10	ortho-, para-Dimethylcyclohexanes (cis and trans)	ortho- and para-xylenes	[98]
11	Cyclohexylcyclopentane	Phenylcyclopentane	[99]
12	Cyclohexylcyclopentylmethane	Phenylcyclopentylmethane	[98]
13	Cyclohexylcyclopentylethane	Phenylcyclopentylethane	[100]
14,15	Dicyclohexyl; decalin	Diphenyl; naphthalene	[101,102]
16, 17	Dicyclohexylmethane; dicyclohexylethane	Fluorene; phenanthrene	[92,103]
18, 19	Diphenylmethane; diphenylethane	Fluorene; phenanthrene	[92]
20	Stilbene	Phenanthrene	[103]
21	Cyclohexylcyclopentylmethane	Phenanthrene	[107]
22,23	Dicyclohexylamine and diphenylamine	Carbazole	[92]
24, 25	Hexahydrobenzoic acid and its esters	Benzoic acid and its esters	[104]
26	Octahydrindene	Hydrindene (indane)	[103]
27,28	Octahydro- and dihydroanthracene	Anthracene	[108]
29, 30	Carane; pinane	Cymene	[105]
31	Thujane	Dimethylisopropylcyclopentane	[105]
32, 33	Fenchane; isobornylane	No change	[105]
34	Cyclofenchene	α- and β-Fenchenes	[105]
35	Gem-dimethylcyclohexane	Either no change or conversion into toluene and xylenes	[95,110, 96]
36, 37	Cyclopentane; methylcyclopentane	No change	[84]
38, 39	n-Hexyl-, n-octylcyclopentane	No change	[106]
40, 41	Dicyclopentyl; 3,3'-dimethyldicyclopentyl	No change	[101]
42	Phenylcyclopentylmethane	No change	[98]
43	Dicyclopentylethane	No change	[106]
44	Methylcyclopentanecarboxylic acid	No change	[104]
45	Cycloheptane	No change	[87]
46	Cyclo-octane	Bicyclo-octane and methylcycloheptane	[45]
47	Benzobicyclononene	Diphenylmethane and fluorene	[109]

phthalic acids [117]:

$$3C_6H_8(COOCH_3)_2 \longrightarrow C_6H_4(COOCH_3)_2 + 2C_6H_{10}(COOCH_3)_2.$$

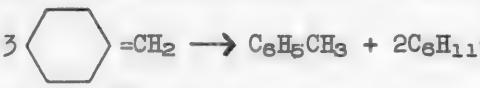
In the intermediate stage of saturation one and the same substance acts as donor and acceptor of hydrogen in this process.

N.D.Zelinsky later established that passing cyclohexene over palladium at 164° converts all of it into a mixture of cyclohexane and benzene [118]; the percentage composition of the mixture rigorously conforms to the following equation:



Zelinsky called this reaction, involving the redistribution of hydrogen among several molecules of an unsaturated cyclic compound, "irreversible catalysis", inasmuch as it was impossible to recover the cyclohexene from the cyclohexane catalytically, no matter what conditions were used. The irreversible catalysis of cyclohexene is almost complete even at room temperature [118], though the process is much slower than when heat is used.

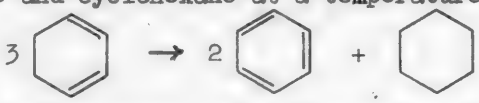
Zelinsky studied the phenomenon of irreversible catalysis in the isomeric methylcyclohexenes and in methylenecyclohexane – a hydrocarbon with a semicyclic double bond [120]:



$$3\,C_6H_{10}{=}CH_2 \longrightarrow C_6H_5CH_3 + 2C_6H_{11}CH_3.$$

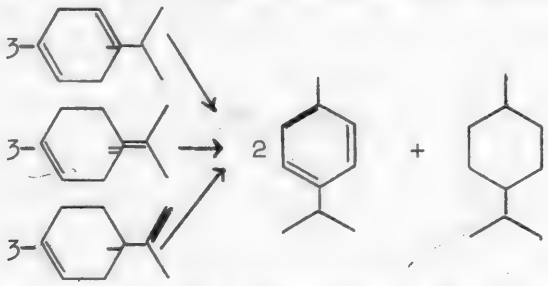
Other homologs of cyclohexene [118] and unsaturated condensed bicyclic hydrocarbons (Δ^2-dihydronaphthalene [118] and octohydronaphthalene [121] are also irreversibly catalyzed readily and completely.

Cyclic hydrocarbons with two double bonds are irreversibly catalyzed with the greatest ease. Cyclohexadiene, for example, is converted over palladium into a mixture of benzene and cyclohexane at a temperature as low as 91° [118]:



To his associates and students, N.D.Zelinsky used to demonstrate a striking experiment of the conversion of the 1,3- and 1,4-cyclohexadienes in the cold above palladium: as soon as the palladium was placed in the cyclohexadiene, which had been chilled to −20°, the hydrocarbon began to boil up violently at once, all of it being converted into a mixture of benzene and cyclohexene [122].

Zelinsky later investigated the behavior of many terpene hydrocarbons in irreversible catalysis. He showed that terpinene, terpinolene [123], and limonene [124] are converted (by catalysis with palladium) into identical mixtures of cymene and menthane:



Thus it was found that different positions of one of the two double bonds – inside the ring or outside it [120,123,124] – had no effect upon the irreversible catalysis of unsaturated cyclic hydrocarbons with six-membered rings.* Bicyclic terpene hydrocarbons with a double bond inside the ring or outside it (α-pinene [126], β-pinene [123], thujene [127], and even saturated bycyclic hydrocarbons with a three-membered ring: carane [128]) are also readily catalyzed irreversibly.

It should be pointed out that unsaturated hydrocarbons with six-membered rings that are not hydroaromatic (1,3,3-trimethylcyclohexene [128]) do not undergo any

*Cyclopentene undergoes a very slight (2 to 5%) hydrogen disproportionation reaction above oxide catalysts (at 450-500°) and above palladium (at 200°) [125].

change in irreversible catalysis; unsaturated hydrocarbons with six-membered rings and an endo-methylene bridge (α-fenchene) are also unaffected by palladium catalysis [128].

N.D.Zelinsky's irreversible catalysis – this interesting and singular catalytic reaction involving the redistribution of hydrogen – was subsequently the subject of a comprehensive study by R.Ya.Levina. In her continuation and extension of N.D. Zelinsky's work, R.Ya.Levina found that irreversible catalysis affects not only those cyclic systems with six-membered rings in which the double bond is in the ring or is semicyclic, but also those containing double or even triple bonds in the side chain, no matter how far removed from the ring [129-131]. Vinyl- and allylcyclohexanes, 4-cyclohexylbutene-1, 5-cyclohexylpentene-1, cyclohexylethyne, 3-cyclohexylpropyne-1, 4-cyclohexylbutyne-1, and 5-cyclohexylpentyne-1 [129], as well as vinylcyclohexene [130,131] and allylcyclohexene [129], are converted over platinum with equal ease, each of them giving rise to the respective homologs of benzene and cyclohexane, such as:

$$3C_6H_{11}CH_2CH_2CH_2CH{=}CH_2 \longrightarrow C_6H_5C_5H_{11} + 2C_6H_{11}C_5H_{11}$$

$$3C_6H_{11}CH_2CH_2CH_2C{\equiv}CH \longrightarrow 2C_6H_5C_5H_{11} + C_6H_{11}C_5H_{11}.$$

A cyclohexene hydrocarbon with a triple bond in the side chain – 1-ethynylcyclohexene-1 – is irreversibly isomerized to ethylbenzene over platinum at 200° [136]:

$$-C{\equiv}CH \longrightarrow C_6H_5C_2H_5.$$

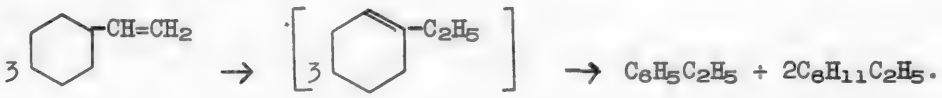
R.Ya.Levina also discovered that when catalyzed with platinum at 205°, decalin hydrocarbons with unsaturated side chains – the cis and trans forms of β-allyldecalins and 4-β-decalylbutenes-1 – behave like their analogs in the cyclohexane series, the steric arrangement of the carbon atoms having no effect upon the process of irreversible catalysis [132]. For instance,

$$5C_{10}H_{17}CH_2CH_2CH{=}CH_2 \longrightarrow 4C_{10}H_{17}C_4H_9 + C_{10}H_7C_4H_9.$$

The presence of a branched side chain in the cyclohexane hydrocarbon does not interfere with the irreversible catalysis [133]:

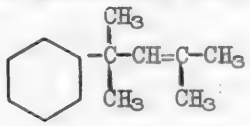
$$3C_6H_{11}CH_2CH{=}C\begin{matrix}CH_3\\CH_3\end{matrix} \longrightarrow 2C_6H_{11}CH_2CH_2CH\begin{matrix}CH_3\\CH_3\end{matrix} + C_6H_5CH_2CH_2CH\begin{matrix}CH_3\\CH_3\end{matrix}.$$

All these complicated transformations were explained by R.Y.Levina as due to the fact that two reactions occur consecutively: first, the shift of the double bond from the side chain to the ring, and then the irreversible catalysis of the resulting cycloalkene [134]:



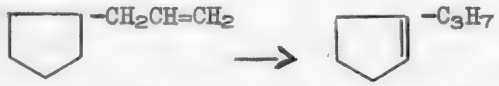
$$3\ -CH{=}CH_2 \rightarrow \left[3\ -C_2H_5\right] \rightarrow C_6H_5C_2H_5 + 2C_6H_{11}C_2H_5.$$

The correctness of this equation was demonstrated by the fact that irreversible catalysis does not occur when the double bond is separated from the ring by a "barrier" of a quaternary carbon atom and hence cannot shift to the ring:



$$-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH{=}C\begin{matrix}\\CH_3\end{matrix}-CH_3 \longrightarrow \text{no change.}$$

The reality of the intermediate stage in the foregoing equation – the shift of the double bond to the ring under the action of the contact agent – was again confirmed by the recent contact isomerization of several alkenyl cyclopentanes and alkenyl cyclohexanes into the respective 1-alkyl cyclopentenes-1 and 1-alkyl cyclohexenes-1 [135], such as:



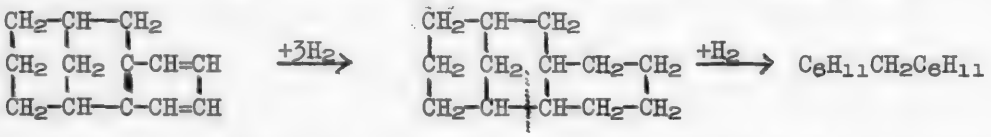
Thus the systematic research of N.D.Zelinsky and his pupils on the behavior of many unsaturated monocyclic and bicyclic hydrocarbons with six-membered rings and with one or more double bonds in the ring and with a double or triple bond in a side chain (no matter how far from the ring) during catalysis with platinum or palladium enabled them to reach the important conclusion that the ability to undergo irreversible catalysis is a universal and typical property of all the types of hydrocarbons mentioned.

Some of N.D.Zelinsky's discoveries in catalytic hydrogenation are of great importance. As far back as 1898, Zelinsky employed the catalytic action of palladium to reduce halogen compounds; employing palladinized zinc and hydrochloric acid, he readily reduced halides to hydrocarbons [136].

In 1911-1912 Zelinsky proved, for the first time, that contrary to Sabatier's assertions, platinum and palladium are excellent catalysts for the hydrogenation of benzene and its homologs [84,137]. Later, Zelinsky was the first to employ nickel on aluminum oxide in hydrogenation [88]; this catalyst, like platinum and palladium, is widely used at the present time. Zelinsky subsequently found that other metals: iridium, rhodium, ruthenium [85,138], and osmium [138,139] can be successfully used for catalytic hydrogenation.

A.M.Rubinshtein [140] and N.I.Shuikin [141] have recently described the employment of low-percentage platinum and nickel catalysts (on charcoal) for the hydrogenization of benzene, alkenes, and cycloalkenes in the vapor phase. B.A.Kazansky [142] has effected the rapid hydrogenation of alkenes at room temperature by using low-percentage platinized charcoal; N.D.Zelinsky [143] had previously used catalysts thus activated to hydrogenate ketones.

His study of the catalytic hydrogenation of hydrocarbons of various structures (and of their derivatives [97-103,105] enabled Zelinsky to make many new contributions in this field. He found that hydrogenating xylenes above osmium or nickel may be used as a method of preparing the <u>cis</u> or the <u>trans</u> form, respectively, of the dimethylcyclohexanes [96]; naphthalene is hydrogenated over osmium, forming pure <u>cis</u>-decalin [138]. Zelinsky described the catalytic hydrogenation of some bicyclic and tricyclic bridged hydrocarbons containing a three-membered ring [51,105], as well as an interesting tricyclic hydrocarbon, benzobicyclonene [144]:



The catalytic hydrogenation of cyclopentane hydrocarbons with ring cleavage, discovered by N.D.Zelinsky and B.A.Kazansky in 1933 in methyl-<u>endo</u>-methylenecyclohexane, which was converted into a mixture of paraffin hydrocarbons at 300-310° by platinized charcoal and hydrogen, is exceptionally interesting [145]. This conversion was explained as the cleavage of the five-membered ring of methyl-<u>endo</u>-methylenecyclohexane during the first stage of hydrogenation, giving rise to

homologs of cyclopentane, which are then hydrogenated to paraffins [145]:

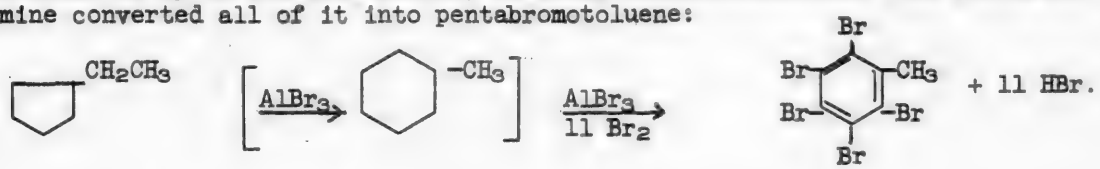
The correctness of this explanation of the reaction was proved by the fact that under these same conditions cyclopentane is wholly converted into normal pentane [145]. It was also found that mono-alkyl cyclopentanes (methyl-, ethyl-, and propyl-pentanes) are easily opened during hydrogenation, the resulting paraffins being of iso, rather than normal structure [146,147]. The astonishing phenomenon of the cleavage of the five-membered ring during hydrogenation at 300-310°, which had been previously held to be impossible, was subsequently investigated by Zelinsky's associates under his supervision, using many cyclopentane hydrocarbons [148-153, 55,89, 63] and their derivatives (S.S.Novikov) [154], as well as by B.A.Kazansky and his associates [155]. In recent years B.A.Kazansky has investigated the deeper hydrogenolysis of five-membered rings (cyclopentane, methyl-, dimethyl-, and isopropyl cyclopentanes, and endo-methylenecyclohexane) and has discovered the basic laws governing this process - the location of the rupture of the C—C bond in the hydrocarbons of the cyclopentane series and the effect of the number and position of substituents upon the course and rate of the reaction [156]. It was found that it is chiefly the C—C bond one carbon atom away from the carbon atoms having substituents that is hydrogenolyzed; the accumulation of methyl groups in a homolog of cyclopentane slows down the reaction [156]. B.A.Kazansky likewise made a study of the reaction when carried out under pressure [157] and of the possibility of employing other catalysts than platinum [158].

The new reaction discovered by N.D.Zelinsky and B.A.Kazansky - the opening of a five-membered ring by hydrogenation at 300-310°, which is as characteristic a reaction for the cyclopentanes by now as catalytic dehydrogenation is for the cyclohexanes, overthrew the long-established concept of the exceptional stability of the five-membered ring and established a direct connection between two classes of hydrocarbons that had been separate and distinct up to that time: the pentamethylenes and the paraffins. B.A.Kazansky's researches in this field won him the Stalin Prize in 1949.

It should be noted that the hydrogenation cleavage of the four-membered ring in the homologs of cyclobutane likewise results in the formation of iso-paraffins, as S.E.Raik has pointed out [159].

The phenomena of stereoisomerism and isomerism have always interested N.D. Zelinsky profoundly. As far back as his dissertation for his Doctor of Science degree [160] (1891) and in other individual papers [161]*, Zelinsky reported his researches on the stereoisomerism of dibasic and tribasic acids. Subsequently, Zelinsky and his pupils devoted many papers to a study of the isomeric and stereoisomeric conversions of cyclic and acyclic hydrocarbons under the action of aluminum halides or of contact agents consisting of metals or metal oxides.

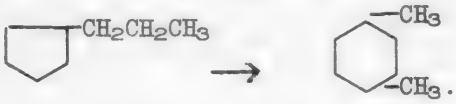
In 1905 N.D.Zelinsky [163] discovered a remarkable reaction - the isomerization of a cycloparaffin containing five atoms in the ring to another containing six when acted on by an aluminum halide; reacting ethylcyclopentane with $AlBr_3$ and bromine converted all of it into pentabromotoluene:



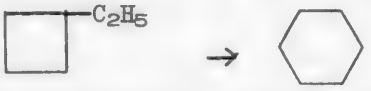
* L. A. Chugayev [162], a pupil of N. D. Zelinsky, took part in these researches.

As N.D.Zelinsky put it [163], " In this reaction, therefore, we see the isomerization of the ethylpentamethylene ring into the methylhexamethylene ring, an aromatic derivative of which is pentabromotoluene." But for a long time this reaction remained unused, even forgotten, though it convincingly showed that Aschan's work on the partial isomerization of cyclohexane to methylcyclopentane under the action of $AlCl_3$ was based upon an incorrect assumption, unconditionally derived from the strain theory. In 1934 N.D.Zelinsky's reaction was reproduced by E.M.Tarasova, who secured tetrabromo-p-xylene from 1,2-methylethylcyclopentane [164]. In 1934-1937, Yu.K.Yuryev and R.Ya. Levina, in the course of their study of the cracking of diphenyl, decahydroanthracene, dicyclohexyl, and dicyclopentyl with $AlCl_3$ in Zelinsky's laboratory, showed that aluminum chloride exerts an isomerizing as well as a cleaving effect upon cyclic forms under these conditions and established a number of laws governing this isomerization: the cyclohexane ring resists the isomerizing action of aluminum chloride more than does the cyclopentane ring; the higher homologs of cyclopentane are more readily isomerized to six-membered rings than the first member of the series - methylcyclopentane - that can undergo such isomerization [165].

These researches were a guide in the correct solution of the problems of isomerizing the cycloparaffins with $AlCl_3$, and they were fully collaborated in the subsequent research of M.B.Turova-Polyak in 1939; the action of $AlCl_3$ upon ethylcyclopentane and 1,2-dimethylcyclopentane isomerized them practically 100% to methylcyclohexane, while n-propyl-, isopropyl-, n-butyl-, and n-amylcyclopentanes were isomerized into homologs of cyclohexane, as in:



When $AlCl_3$ acts upon ethylcyclobutane, on the one hand, or upon cycloheptane, methyl- and ethylcycloheptane, and cyclo-octane, on the other, they are isomerized into cyclohexane or its homologs, repsectively [167], which is a striking illustration of the general tendency of various cycloparaffins to be transformed into the six-membered system of cyclohexane, which is stable under these conditions:



N.D.Zelinsky likewise showed that $AlCl_3$ or $AlBr_3$ changes the spatial configuration of bicyclic hydrocarbons: the cis forms of decahydronaphthalene and hydrindene are converted into the trans forms [168].

N.D.Zelinsky also effected isomeric and stereoisomeric conversion of cyclic forms, using metals and metal oxides as contact agents.

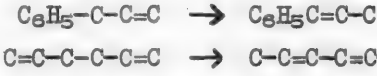
The stereoisomeric transformations of cyclic hydrocarbons include, for example, the conversion of cis-o-dimethylcyclohexane into the trans form by catalysis with nickel [98]. It is worthy of note that contact with palladium also effects the conversion of methyl maleate into methyl fumarate [169].

N.D.Zelinsky and Yu.A.Arbuzov further showed that cycloalkenes - cyclohexene, 1-methylcyclohexene-3, menthene, and cycloheptene - are isomerized into contracted rings by contact with metal oxides at 400-450°, [170 171]:

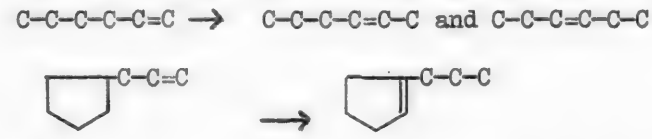
The alkenes – heptene-1 and octene-1 – also undergo nuclear isomerization under these conditions [172].

In 1929, N.D.Zelinsky and R.Ya.Levina discovered the isomerization of an alkene-1 to an alkene-2 by contact with palladium [173]:

The research of R.Ya.Levina on the contact isomerization of unsaturated hydrocarbons involving a shift of their multiple bond constituted a continuation and extension of this reaction. Platinum, palladium [174], and metallic oxides were used as the isomerizing contact agents. Aromatic hydrocarbons with unsaturated side chains (allylbenzene, allyltoluenes, diallylbenzene, α-allylnaphthalene, 4-phenylbutene-1, 5-phenylpentene-1, and others) and diene hydrocarbons of the isolated type (diallyl, diisobutenyl, 2-methylpentadiene, and others) are readily isomerized by contact with metallic oxides at 250° [175]; the double bond is shifted from the end of the carbon chain into its interior, giving rise to homologs of styrene and homologs of divinyl, respectively:



The latest researches of R.Ya.Levina have shown that the alkenes-1 are readily isomerized over an activated contact agent, the double bond being shifted into the interior of the carbon chain, while cyclic hydrocarbons with unsaturated side chains are isomerized by the double bond shifting to the ring [176], as in:



The phenomenon of contact isomerization has proved to be typical of the alkynes as well; in contact with metallic oxides the alkynes are isomerized in two ways: with the triple bond shifted from the end of the chain into the latter's interior, and with the triple bond converted into two conjugated double bonds [177]:

Thus, the researches of Zelinsky and his pupils on the contact isomerization of hydrocarbons directly connected hydrocarbons of different classes: the cycloalkanes and cycloalkenes having five-membered rings with those having six-membered rings; the alkenyl benzenes with the styrenes; the dienes of the isolated type and the alkynes with the conjugated dienes, etc.

The contact conversions of the hydrocarbons are, to be sure, a favorite topic of N.D.Zelinsky's, but the compass of Zelinsky's interests was so wide than the hydrocarbons alone could not absorb them entirely.

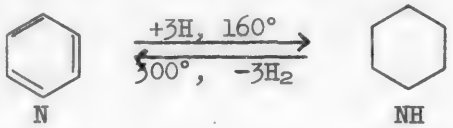
The heterocyclic compounds, of interest because of their reactivity and their existence in nature and in substances that are so important in biology, likewise evolked Zelinsky's interest from the early days of his scientific career. In his thesis for the degree of Master of Science (1889), entitled "The Problem of Isomerism in the Thiophene Series" [178], the object of which was a study of the polybasic acids of the thiophene series and establishing their isomerism, Zelinsky

prepared homologs of thiophene: α,β-dimethylthiophene; α-methyl-β-ethylthiophene; β,β'-dimethylthiophene; and α,β,β'-trimethylthiophene, which he oxidized to the respective acids, comparing the latter with the acids produced by different methods. That is how N.D.Zelinsky established the structure of the isomeric polybasic acids of the thiophene series.

Many years later, Zelinsky returned to the heterocyclic compounds, being interested in their behavior in catalytic hydrogenation and dehydrogenation. Using the catalysts he had already tested – platinum, palladium, and osmium, deposited on charcoal or asbestos – he was the first to demonstrate the feasibility of smoothly hydrogenating pyridine and α-picoline [179], pyrrole and α-methylpyrrole [180], and α-methylfuran [181] to their complete hydrides. An endeavor to hydrogenate thiophene led Zelinsky to develop the catalytic desulfurization of petroleum distillates (vide infra).

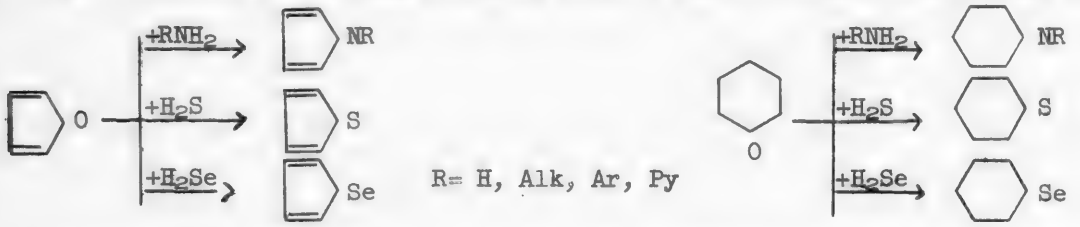
The hydrogenation of heterocyclic systems, at ordinary as well as at high pressures, was continued by N.D.Zelinsky's pupils: M.I.Ushakov [182] in the pyridine series; N.I.Shuikin [183] in the furan series; and Yu.K.Yuryev [184] in the furan, pyrrole, and quinoline series.

N.D.Zelinsky further demonstrated that the completely hydrogenated heterocyclic compounds containing nitrogen, with five- and six-membered rings: piperidine and α-pipecoline [179], pyrrolidine and N-methylpyrrolidine [180], are dehydrogenated with the same catalysts when the temperature is raised to 260-300°, yielding the respective compounds of the pyridine or pyrrole groups:

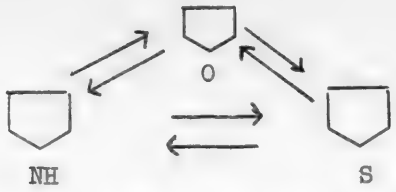


These researches of N.D.Zelinsky were continued by Yu.K.Yuryev, who showed that Zelinsky's catalytic dehydrogenation applies not only to the N-ethyl- and N-propylpyrrolidines [184] and decahydroquinoline [184], but also to tetrahydrothiophene [185], which is converted into thiophene by the detachment of four atoms of hydrogen.

The general interest displayed by N.D.Zelinsky himself and his university laboratory in the catalytic reactions of heterocyclic compounds is reflected in the research of Yu.K.Yuryev, who discovered (in 1936) and worked out in detail the catalytic transformation of heterocyclic compounds containing oxygen of the furan series: furanidine (tetrahydrofuran), Δ^2-dihydropyran, and tetrahydropyran, into cyclic compounds with different hetero atoms. The reaction involves the following: when heterocyclic compounds containing oxygen are reacted at high temperature with ammonia, amines, hydrogen sulfide, or hydrogen selenide, using aluminum oxide as the contact agent, the oxygen atom is replaced by nitrogen, sulfur, or selenium, and we get compounds containing nitrogen, sulfur, and selenium, respectively [186]:

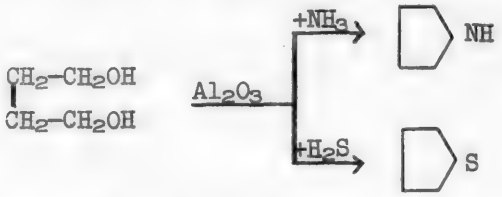


Yu.K.Yuryev likewise established the contact conversion of aromatic and saturated heterocyclic compounds with five-membered rings [187]:

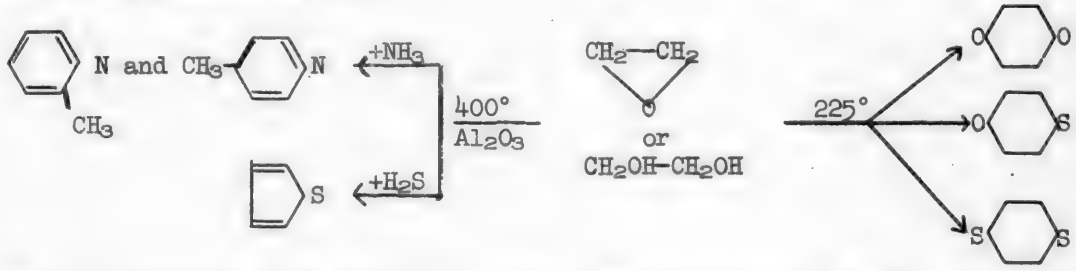


These reactions for the first time established the genetic links of furan, pyrrole, and thiophene, as well as the general trend of the reaction: from rings containing oxygen to rings with other hetero atoms, which establishes the importance of this reaction in biology.

It was further shown that heterocyclic compounds can be conveniently prepared from 1,4- or 1,5-diols by reacting them with ammonia or hydrogen sulfide and $AlCl_3$ [188]:

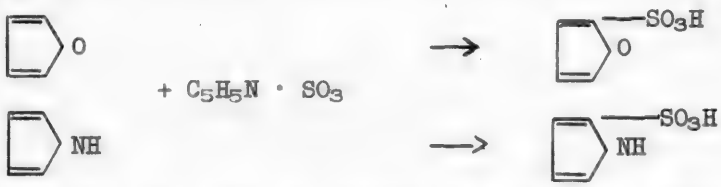


Ethylene oxide and ethylene glycol yield saturated heterocyclic compounds with six-membered rings and with two hetero atoms in the 1,4-position when reacted with hydrogen sulfide and $AlCl_3$ as the contact agent at 225°: 1,4-dioxane; 1,4-thioxane; and 1,4-dithiane; at 400° this reaction yields thiophene, while reaction with ammonia yields α- and β-picolines [189]:



These researches of Yu.K.Yuryev won him a Stalin Prize in 1946.

We cannot pass by another series of researches, carried out in N.D.Zelinsky's laboratory. A.P.Terentyev discovered the feasibility of sulfonating such acidophobic heterocyclic compounds as furan, pyrrole, and indole. Sulfonation was effected smoothly and simply by reaction with bound sulfur trioxide: pyridine sulfotrioxide. Sulfo acids of furan, pyrrole, and indole and their homologs were prepared in this manner [190]:



It has been shown that this sulfonation is also quite applicable to diene hydrocarbons – butadiene, α-phenylbutadiene, and styrene [191]:

$$CH_2{=}CH{-}CH{=}CH_2 + C_5H_5N{\cdot}SO_3 \longrightarrow CH_2{=}CH{-}CH{=}CH{\cdot}SO_3H$$
$$C_6H_5CH{=}CH_2 + C_5H_5N{\cdot}SO_3 \longrightarrow C_6H_5CH{=}CH{\cdot}SO_3H$$

These researches of A.P.Terentyev won him a Stalin Prize in 1948.

The Chemistry of Petroleum

When we analyze the creative career of N.D.Zelinsky, tracing his numerous and diversified researches on the synthesis and transformations of hydrocarbons, and compare then with his researches on petroleum, it becomes clear that these researches are interrelated, supplementing and explaining one another, constituting a single whole. N.D.Zelinsky provided his own original and fundamental answers of outstanding significance to several cardinal problems of petroleum chemistry: researches on the chemical constitution of petroleum, a search for new methods of processing petroleum, and tracing the origin of petroleum.

The work of Russian chemists, dating from the eighties of the last century, laid the foundations for our knowledge of the composition of Caucasian petroleum. The road they traversed led from the recovery of the individual hydrocarbons from petroleum to the synthesis of hydrocarbons of the same composition and structure and the establishment of the identity of the two. Both of these paths were extremely difficult. The individual hydrocarbons, recovered as the result of painstaking work, were then converted into their derivatives, which were then carefully purified.

Synthesis of hydrocarbons that were identical with the naphthenes of Caucasian petroleum was an even more difficult task, inasmuch as the method then available to research workers – reducing the homologs of benzene with hydriodic acid – yielded a mixture of hydrocarbons. Moreover, though the identity of the synthetic hexahydrobenzenes with the naphthenes was established in principle (and was confirmed by the fact that the latter belonged to the alicyclic series), the problem of the structure of the ring remained moot. Only after the individual hexahydrobenzenes had been produced by a purely synthetic method could this problem be resolved.

The synthesis of dimethylcyclohexane from dimethylpimelic acid effected by N.D.Zelinsky [2] and described above, provided the first wholly reliable standard of comparison with the 118-120° fraction of Caucasian petroleum – the so-called octonaphthene. The results of the enormous work performed by Zelinsky and his pupils on the synthesis of a large number of naphthenes have been cited above.

Comparing the synthetic octonaphthene (dimethylcyclohexane) with the natural petroleum product showed that the latter contains some lighter hydrocarbon of the same composition. It was natural to assume the presence of a hydrocarbon of the most stable alicyclic form – a homolog of cyclopentane – inasmuch as V.V Markovnikov had long ago proved that cyclopentane and, hence, methylcyclopentane, was present in the 50-52° and 70-72° fractions of Caucasian petroleum. Zelinsky therefore did much research on the cyclopentane hydrocarbons.

Toward the end of the past century, it had been established that the principal constituents of petroleum were hydrocarbons of three major classes: paraffins, naphthenes, and aromatics, and that the naphthenes in Caucasian petroleum were hydrocarbons of the cyclopentane and cyclohexane series. Once we were able to divide petroleum hydrocarbons into classes, the research problem would become considerably more simple. The aromatic hydrocarbons were removed completely by strong sulfuric acid, while Zelinsky outlined a new way of separating the naphthenes and the paraffins in 1898: converting the alicyclic hydrocarbons of the cyclopentane and cyclohexane series into ketones by reacting them with a previously prepared coordination compound of acetyl chloride and anhydrous aluminum chloride or bromide [182]:

$$C_6H_{12} + CH_3COCl...AlCl_3 \rightarrow C_6H_{11}COCH_3 + HCl + AlCl_3.$$

Comparison of the ketones secured from the natural naphthenes with the synthetic ketones provided an idea of the nature of the cyclanes recovered from the petroleum.

Returning to this topic after an interruption of many years, Zelinsky used the example of the individual cycloparaffins of the penta- and hexamethylene series to prove that, contrary to the views held by some authors, these cyclic compounds are not isomerized when ketonized by the Zelinsky reaction. The Zelinsky method yielded, in the main, unsaturated ketones: methylcyclopentane yielded nothing but 1,2-methylacetylcyclopentene [193]; the usual Friedel-Crafts reaction yielded a mixture of two ketones - a saturated and an unsaturated one. Inasmuch as E.M.Tarasova [194] had established, moreover, that paraffins are not acetylated by the Zelinsky method, it was apparent that the Zelinsky reaction could be employed to separate the naphthenes from the paraffins, and could also serve as a method for synthesizing cycloparaffinketones with a carbonyl group in the side chain.

As part of the same program of petroleum research and the utilization of petroleum hydrocarbons, N.D.Zelinsky had demonstrated as far back as 1902 that chlorinated naphthenes react readily with magnesium, provided the latter was activated with iodine or an aluminum halide. This was the first use of chlorides in syntheses with organomagnesium compounds. From the resulting organomagnesium compounds of the naphthenes Zelinsky produced naphthenic alcohols and naphthenic acids [195]. By reacting the naphthenic acids with glycerol Zelinsky produced a new type of fats - glycerides of the naphthenic acids.

N.D.Zelinsky always insisted that the petroleum hydrocarbons, which nature gives to us in the ready state, diversified in chemical structure and in composition, can and should be rationally exploited by converting them into highly valuable chemical compounds. This explains Zelinsky's extraordinary interest in the pyrogenic aromatization of petroleum as an industrial method of producing reactive aromatic hydrocarbons.

In the nineties, Zelinsky took an active part in tackling this problem, developing the chemical aspect of pyrogenic aromatization by the method due to the engineer A.Nikiforov [196], who perfected the process originated by A.Letny [197]. Zelinsky demonstrated that it was technically possible to produce aromatic hydrocarbons - benzene and toluene - from petroleum, and at the beginning of the nineties the first pyrogenic plant in Russia was in operation near Kineshma, producing nitrobenzene, aniline, etc. During the First World War, Zelinsky played an active part in the construction and placing in operation of pyrogenic plants in the Caucasus. Thus, N.D.Zelinsky is one of the pioneers of the industry devoted to the pyrogenic aromatization of petroleum in our country.

The pyrolysis of petroleum has one disadvantage, however - the low yield of aromatic hydrocarbons from the petroleum distillates used. This could not satisfy Zelinsky, of course, who was looking for better ways of utilizing petroleum distillates and for an answer to the problem of the mechanism involved in this formation of aromatic hydrocarbons: are acetylene and its homologs first formed, then condensing into the aromatic hydrocarbons, or is the reaction simpler, involving dehydrogenation of the naphthenes with six-membered rings present in the petroleum, which yield benzene and its homologs after the six hydrogen atoms have been detached?

N.D Zelinsky discovered the solution to these problems - both the theoretical and the practical ones - in catalytic dehydrogenation. Using the catalysts he had discovered (platinum, palladium, and later nickel on alumina) to dehydrogenate the 100-104° petroleum fraction, which contained methylcyclohexane, Zelinsky found [198] that after catalysis this fraction contained as much as 50% of toluene. After the toluene had been removed with sulfuric acid, the constants of the dearomatized residue were found to be close to those of ethylcyclopentane.

Thus, catalytic dehydrogenation became the method for aromatizing petroleum fractions that contained hexahydroaromatic hydrocarbons, as shown by Zelinsky and

Yu.K.Yuryev in their catalytic aromatizing of fractions of Perm gasoline (as well as other gasolines : Grozny, Kalinsk, Bibi-Eibat, Sterlitamak, and Novobogatinsk), and particularly by their aromatization of the narrow 100-102° and 119.5-121.4° fractions of Surakhany gasoline, which upon catalysis yielded 68.5% of toluene and 51.5% of xylene, respectively [199].

N.D.Zelinsky and N.I.Shuikin [200] then made a detailed and comprehensive study of the catalytic aromatization of Novobogatinsk gasoline and of various fractions of Surakhany gasoline:" Study of the principal factors affecting the genesis of the deposited dehydrogenating catalysts enabled us to find the optimum conditions for preparing a highly active form, with reproducible properties." N.I. Shuikin and S.S.Novikov also made a detailed study of the causes underlying the inactivating action of cyclanes and cyclenes with five-membered rings upon a platinum catalyst [201].

Catalytic dehydrogenation was also an uncommonly good method for investigating the chemical composition of petroleum fractions, which made it possible to separate the hexahydro aromatic hydrocarbons (the naphthenes with six-membered rings) from the cyclopentane and paraffin hydrocarbons. The naphthenes with six-membered rings are dehydrogenated, and the resulting aromatic hydrocarbons are removed with sulfuric acid. This method has been widely adopted in practice in investigating the chemical constitution of petroleum. N.D.Zelinsky and his co-workers used this method to investigate Urals [202], Perm [199], Sterlitamak [203], Koschagyl [204], and Fergana [205] petroleums, while Yu.K.Yuryev used it to investigate Ukhtinsk [206], Changyrtash [207] Kalinsk [208], Surakhany [209], Shorsinsk [210], Khaudag [210], and Ishimbaev [210] petroleums, the fractions boiling up to 300° also being dehydrogenated.

The feasibility of obtaining accurate results when using catalytic dehydrogenation to investigate the composition of petroleum fractions was demonstrated in researches by N.D.Zelinsky and R.Ya.Levina [211], R.Ya.Levina [212], and Yu.K. Yuryev [213] on artifically prepared fractions consisting of the individual hydrocarbons. These researches convincingly proved that pentamethylenic hydrocarbons are not at all affected under these conditions, although they can be catalytically hydrogenolyzed (vide supra).

This is the proper place to note the excellent work of N.D.Zelinsky and B.A. Kazansky on the condensation of acetylene with activated charcoal at 600-650°, the condensate output being 74%, and the condensate containing 35% of benzene [214].

The problem of the desulfurization of petroleum distillates was one of the petroleum problems dealt with in N.D.Zelinsky's laboratory, and in 1932-1933 Zelinsky and I.N.Tits succeeded in effecting the catalytic desulfurization of petroleum and shale oils without the use of high pressure or temperature [215].

Special mention should also be made of the cracking of petroleum oils with anhydrous aluminum chloride, developed by N.D.Zelinsky in 1918-1919, when Moscow was cut off from Baku and Grozny by the Civil War. This method was used in 1919 for the production of aviation gasoline for the Red Army from the then available reserves of solar oil. The gasoline yield was 63% [216]. In subsequent years the feasibility of converting Emba gasoline, paraffin, ceresin, and the wash tars of gas works into gasoline has been demonstrated [217]. N.D.Zelinsky investigated the mechanism of the reaction by cracking the individual substances - naphthalene, decalin [218], octahydroanthracene [217], and oleic acid [211]- with aluminum chloride, while R.Ya.Levina and Yu.K.Yuryev explored the cracking of diphenyl, dicyclohexyl, decahydroanthracene, and dicyclopentyl [165].

Devoting so much of his research to petroleum, N.D.Zelinsky could not ignore the complicated question of its origin, and followed his own singular path toward solving it. In his papers devoted to a study of the possible sources of petroleum in nature, Zelinsky paid special attention to Balkhash sapropelite. A dark-brown, rubbery substance, formed from the alga Botriococcu Braunii, sapropelite is deposited in enormous quantities on the shores of Lake Balkhash. According to Zelinsky, sapropelite contains up to 96% of organic matter, more than 42% of it being a mixture of solid organic acids, paraffin, and vegetable wax. Dry distillation of sapropelite yields, in addition to gas and coke, as much as 63% of tar (sapropelol), which in turn, yields gasoline, kerosene, and paraffin upon distillation.

Study of the products of the dry distillation of sapropelite, obtained at relatively low temperature (no higher than 450°) and comparison of them with the natural petroleum products indicated that after the unsaturated hydrocarbons had been eliminated from the sapropelol fractions, the latter proved to be quite similar to the corresponding petroleum distillates. Detailed investigation of the composition enabled him to show that they contain hydrocarbons of three types: aromatic, cycloparaffin, and paraffin, which are also characteristic of natural petroleum. It should likewise be noted that sapropelol is optically active. N.D.Zelinsky thus demonstrated that sapropelite may be the parent substance of petroleum [219]. Zelinsky later undertook a systematic investigation of the production of synthetic petroleums from various raw materials, both animal and vegetable, with aluminum chloride. He studied the decomposition of oleic, palmitic, and stearic acids [220], cholesterol and rosin [221], phytosterol and abietic acid [222], waxes and Bogheads [220], and natural and synthetic rubber [222].

The yield of liquid products was 65-75% in the decomposition of oleic acid, cholesterol, and betulin. Optically active raw materials yielded optically active decomposition products. The distillates of the gasoline and kerosene type resembled the corresponding petroleum distillates.

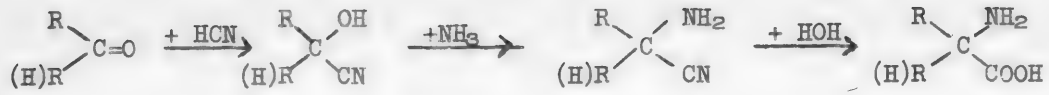
Zelinsky thus demonstrated that under certain conditions a number of substances, of animal or vegetable origin, may serve as the source material for the formation of petroleumlike products, the nature of the parent substance (raw material) governing the peculiarities of composition of the artificial petroleum as is the case with natural petroleums of different types and fields.

In these researches of N.D.Zelinsky's the theory of the organic origin of petroleum received a new, original, and convincing confirmation.

Chemistry of Albumen

From the very beginning of his scientific career N.D.Zelinsky has been deeply interested in biochemistry - the chemistry of the amino acids and proteins. Zelinsky's first paper of general biological significance was his student research on the reaction of methylamine with β-methylglycidic acid, which resulted in the production of β-methylamino-α-hydroxybutyric acid [223]. This research was a continuation of work done by Zelinsky's teacher, Prof. G.Melikov (Melikishivili).

In 1906, desiring to synthesize amino acids from the ketones prepared from petroleum hydrocarbons, Zelinsky evolved a simple cyanohydrin method of synthesizing α-amino acids and gave his own explanation of the mechanism of this reaction:



Together with several of his pupils, N.D.Zelinsky [224] synthesized and studied a large number of amino acids of diverse structure: phenylaminoacetic, aminoisobutyric, cyclohexane aminoacetic, methylcyclopentane aminocarboxylic, cyclohexane aminocarboxylic, methylcyclohexane aminocarboxylic, cycloheptane aminocarboxylic, alanine, n-aminobutyric, β-cyclopropyl-α-aminopropionic, and 1,4-diaminohexahydroterephthalic acids.

Zelinsky then published a method for synthesizing free esters of the α-amino acids that is much superior to all others [225] and, using his cyanohydrin method, he was the first to synthesize the following hydroxy amino acids [226]: δ -hydroxyaminocaproic acid, γ-hydroxy-α-amino-α-methylvaleric acid, δ-hydroxy-α-amino-α-methylvaleric acid, and ε-hydroxy-α-amino-α-methylcaproic acid.

By 1910 the development of protein chemistry came to a stop, since E.Fischer's method of analyzing protein hydrolyzates proved to be useless in some cases, for it was unable to account for as much as 40% of the nitrogen in some proteins, inasmuch as enzymes were unable to hydrolyze them completely. N.D.Zelinsky chose hydrolysis conditions employing an inorganic catalyst that yielded results approaching those of the natural fermentation of proteins: catalysis with weak acids and alkalies, but at higher temperatures than usually employed, and at much higher pressure. This method of the autoclave hydrolysis of proteins, as well as of entire small living organisms, played a significant part in subsequent research in protein chemistry and gave rise to new views of the structure of protein, linked to the diketopiperazine theory of the structure of the protein molecule proposed by Zelinsky in 1914 [227].

In 1923 N.D.Zelinsky and V.S.Sadikov published the results of more than ten years of research on proteins [228] and commented that hydrolysis with weak acids (1% HCl) in an autoclave at 180° is a catalytic hydrolysis, which breaks down the protein molecule principally at its polypeptide links; and that this sort of hydrolysis is very much like fermentative hydrolysis. Zelinsky proved that the products of autoclave hydrolysis include, in addition to the amino acids, a large quantity of cyclic anhydrides (diketopiperazines) of these acids. Eliminating the possibility of secondary formation of the diketopiperazines, Zelinsky was the first to point out the exceptionally great significance of diketopiperazines in building up the complicated protein molecule.

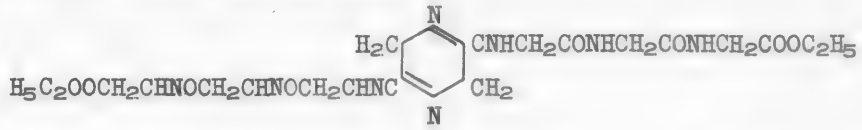
Let us cite some of the findings of N.D.Zelinsky and V.S.Sadikov: After a feather had been hydrolyzed in the autoclave, the ether extract of the hydrolyzate yielded diketopiperazines formed from leucine and valine, glycine and phenylglycine, and leucine and proline; the ethyl acetate extract yielded an anhydride formed from glycine and phenylalanine; and the chloroform extract yielded leucine-alanine, phenylalanine, and leucine-glycine anhydrides [229]. Diketopiperazines were also found after the fermentative cleavage of gelatine and casein, but in smaller quantity than after acid cleavage. Acetic and formic acids also proved capable of hydrolyzing proteins to abiuret products of hydrolysis, in which a large quantity of diketopiperazines was found [230]. In 1927 and N.I.Gavrilov [231] proved that dipeptides are not cyclized in the autoclave at 180°.

Thus, the new method of hydrolyzing proteins and the new method of separating the hydrolyzates by the use of organic solvents discovered by N.D.Zelinsky made it possible to discover in the hydrolysis products a large percentage of diketopiperazines of primary origin. Subsequently, under the overall supervision of N.D.Zelinsky, research on protein chemistry took the following paths: M.M.Botvinnik, M.A.

Prokofiev, and D.A.Morozova made a study of the synthesis and dehydration of β-hydroxy amino acids [232]; they determined the percentage of β-hydroxyamino acids in several proteins, developed a qualitative reaction for the hydroxyamino acids (especially, for serine), and investigated their acylation [233]. A.B.Silaev, as well as M.M.Botvinnik and D.A.Morozova, established the optimum conditions for hydrolyzing proteins [234].

Recent researches, carried out under the direction of one of Zelinsky's pupils, N.I.Gabrilov, have yielded a method for the quantitative determination of the diketopiperazines in protein hydrolyzates by iontophoresis [235] and a method for the quantitative determination of cyclic groups in natural protein by electrolytic reduction [236], the number of the cyclic groups being accurately determined in three proteins: gelatine has 4 amino-acid peptide chains per molecule of diketopiperazine; albumin has 5, and sturin has 6.

In their search for possible forms of links between the diketopiperazines and the amino acids and peptides, N.D.Zelinsky and N.I.Gavrilov effected the synthesis of a model of this type of link - an amidine [237]. A synthetically produced model that exhibited the major protein reactions - the biuret and the picric test - was suggested as a possible micromolecule:



This link is fermented by pepsin and intestinal juices, which proves its applicability to such structures in the protein molecule. This model combines, as it were, the polypeptide and the diketopiperazine theories of protein structure.

The absorption spectra of copper, nickel, and cobalt coordination compounds of peptides of various length and proteins indicated that the protein molecule contains peptide chains, which are no longer than a tripeptide [238]. This research was the cornerstone of the pyrazine-tripeptide theory of protein structure advanced by N.I.Gavrilov as a confirmation and extension of the researches of N.D.Zelinsky.

The researches of N.D.Zelinsky and N.I.Gavrilov in protein chemistry [229] were honored with the highest award - a Stalin Prize, first class - in 1948.

Other biochemical researches of N.D.Zelinsky's included: a study of the biological stimulators of the growth of the paws of the axolotl made by A.B.Silaev in Zelinsky's laboratory demonstrated that hydrolyzates of axolotl gristle, introduced subcutaneously into a specimen, caused it to grow numerous paws [240]; a study of the metallization of organisms - while determining the amount of nitrogen in whole insects, Zelinsky found that reduced red copper ore reproduces all the morphological forms of the insect, furnishing an exquisite model of the specimen [241].

And, lastly, one of Zelinsky's early researches (1891): a study of the origin of hydrogen sulfide zones in the Black Sea. Zelinsky examined specimens of Black Sea ooze and found that the true cause of the formation of hydrogen sulfide is the activity of a species of anaerobic bacteria, which make use of sulfates and sulfites as a source of oxygen in a suitable culture medium, reducing them to hydrogen sulfide. N.D.Zelinsky isolated these bacteria - Bacterium hydrosulfureum Ponticum - in his joint research with Dr. E.M.Brusilovsky [242].

In his researches on the chemical nature and structure of proteins, on hydrogen sulfide fermentation in the Black Sea and the Odessa estuaries, on a Balkhash sapropelite as the parent substance of petroleum, on the biological stimulators of the

growth of the axolotl's paws, N.D.Zelinsky put into practice the concept he has always advocated - that a research chemist should be a naturalist as well.

We cannot fail to make special mention of still another bit of research by N.D. Zelinsky, known to the masses of the people: his work on the activation of charcoal, and the design of the "Zelinsky charcoal gas mask" [243], which saved hundreds of thousands of lives during World War I.

Working with self-denial himself, N.D.Zelinsky carried his associates along with him. His laboratory assistant S.S.Stepanov [244] rendered him outstanding aid in testing samples of charcoal and gas masks in the gas chambers.

We have been unable to cover all the fields in which N.D.Zelinsky has labored in this article, more particularly, to set forth his researches on the production of various kinds of synthetic rubber [245], his work on utilizing the inexhaustible reserves of mirabilite (deposits in the Gulf of Karabugaz of the Caspian Sea) for the production of soda, sodium hydroxide, and sulfuric acid [246], his researches in physical chemistry [247], and his researches on the chemistry of extremely high-pressures. N.D.Zelinsky is the founder of research on chemistry at ultra-high pressures in our country.

The researches of Zelinsky's pupils, A.N.Nesmeyanov and K.A.Kocheshkov, on organometallic compounds, which won them Stalin Prizes, were born and developed in N.D.Zelinsky's laboratory.

The extraordinarily wide range of research, far from completely covered by this survey of ours - extending from the study of the vestiges of life of past epochs: petroleum, through the infinite variety of transformations of an organic substance, to a knowledge of protein - establishes Nikolai Dmitrevich Zelinsky as a naturalist in the broadest and best meaning of the term. His many-sidedness in scientific research combined with eminent personal qualities: his strict gentleness, his impartiality, and his lofty patriotism, have always attracted to Nikolai Dmitrevich numerous pupils, who constitute a world-famous school of organic chemists: the Zelinsky school. N.D.Zelinsky has published scientific papers in association with more than one hundred and forty of his pupils.

Many of Zelinsky's pupils are successfully continuing work on the problems that were called to their attention by him originally, as we have endeavored to show in this survey.

Many an obstacle on the road of chemical transformations has been broken down by Nikolai Dmitrevich and his pupils; long-awaited bridges have been thrown across many abysses which seemed to be impassable in the separation of different classes of organic compounds; exactly as in the fairy tales, many "chemical corpses" have been brought back to life by the miraculous power of catalysis, which Nikolai Dmetrivich Zelinsky established in the field of organic chemistry.

The great Socialist Revolution of October 1917 returned Nikolai Dmitrevich to his beloved University of Moscow; the great Bolshevik Party, the Soviet government, and the great architects of the Soviet state - V.I.Lenin and J.V.Stalin - provided unlimited opportunities for the development of science, and Nikolai Dmitrevich, as a true son of the Russian people, participates in the building of socialism in our country with his untiring creative labors and holds high the banner of advanced Soviet science of the Stalin epoch.

In 1940 N.D.Zelinsky wrote: "Only after the great Socialist Revolution of October did academic life enter an absolutely new channel, which resulted in intensive research starting to boil in the chemistry laboratory too, endeavoring to serve the cause of building a state upon new, just, Socialist foundations" [248]. That is

why Nikolai Dmitrevich Zelinsky had many more pupils, published many more papers, and made a number of outstanding discoveries that have consolidated the leading position of Soviet organic chemistry, in his second Moscow period of activity – his Soviet period, when he was already entering old age, an eminent Soviet scientist, one of the intellectual leaders of organic chemistry.

Nikolai Dmitrevich Zelinsky's name is written in letters of gold in the history of Russian and Soviet science. Teacher of many generations of chemists and naturalists, an outstanding civic worker, Nikolai Dmitrevich Zelinsky is a warm patriot of his great Soviet fatherland, and his scientific achievements are a source of pride to our whole country.

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1 J. Russ. Chem. Soc - Chemical Section of the Russian Physical Chemistry Society.

2 See CB translation p. 505 ff.

3 " " " p. 303 ff.

4 " " " p. 1069 ff.

5 " " " May

6 " " " p. 55 ff.

7 " " " p. 313 ff.

8,9 " " " p. 443 ff.

10 " " " p. a-161 ff.

11 " " " p. 727 ff.

12 " " " p. 265 ff.

13 " " " p. 927 ff.

14 " " " p. 697 ff.

15 " " " p. 693 ff.

16 " " " p. 697 ff.

17 " " " p. a-167 ff.

18,19 " " " p. 173 ff.

20 " " " p. 693 ff.

THE ISOMERIZATION OF UNSATURATED HYDROCARBONS WITH METALLIC OXIDES AS CONTACT AGENTS

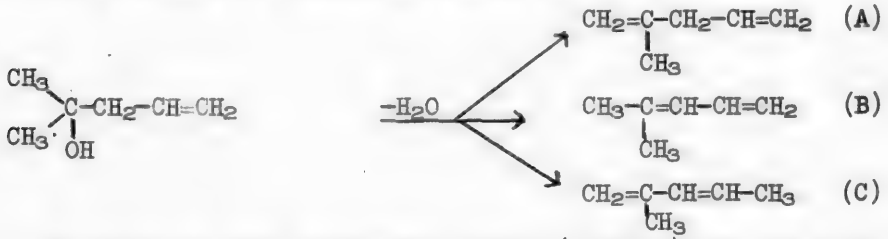
XII. PREPARATION OF METHYLPENTADIENES BY DEHYDRATING DIMETHYLALLYLCARBINOL ABOVE CHROMIUM OXIDE ON ALUMINA

R. Ya. Levina, A. A. Fainsilberg, V. M. Tatevsky, and E. G. Treshchova

A.M.Zaitsev and his pupils were the first to make a study of the dehydration of dimethylallyl carbinol. They showed [1] that using sulfuric acid as the dehydrating agent results in formation of not only the diene hydrocarbon C_6H_{10}, but also of its dimer, $C_{12}H_{20}$. In subsequent papers, V.Nikolsky and A.Zaitsev [2], N.Albitsky [3], and A.Albitsky and V.Nikolsky [4] demonstrated that the principal product of dehydration is either the diene hydrocarbon C_6H_{10} or its dimer, $C_{12}H_{20}$, depending upon the concentration of sulfuric acid employed.

S.N.Reformatsky [5], who made a study of the dehydration of diethylallylcarbinol and dipropylallylcarbinol with sulfuric acid, believed that "when a second double bond is formed, it tries to take a position as far as possible from the existing double bond" [6].

Ya.M.Slobodin dehydrated dimethylallylcarbinol with sulfuric and with oxalic acids [7]. Bacon and Farmer [8] secured a mixture of three isomeric diene hydrocarbons: 2-methylpentadiene-1,4 (A) with a system of isolated double bonds; 2-methylpentadiene-2,4 (or else 4-methylpentadiene-1,3) (B); and 2-methylpentadiene-1,3 (C) with a system of conjugated double bonds:



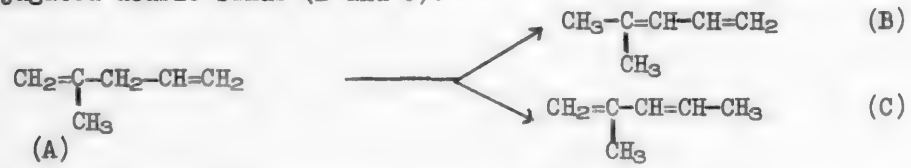
The yield of both conjugated dienes (B and C) was not quite 30% of the theoretical, based on the original carbinol; the rest of the dehydration product consisted

of the diene hydrocarbon (A) with isolated double bonds (over 30% of the theoretical).

In the present research we have employed the contact method of dehydrating dimethylallylcarbinol: dehydration was effected at 250° in the vapor phase above a catalyst – chromium oxide upon alumina.

Fractionation of the resulting mixture of diene hydrocarbons (the yield being 70% of the theoretical under optimum conditions) into a column with 25 theoretical plates yielded 2-methylpentadiene-1,4 (A) (about 11% of the mixture that was fractionated) and a mixture of diene hydrocarbons with conjugated double bonds (B and C) whose boiling points lay close together (about 84% of the mixture used in fractionating, or 59% of the theoretical).

Thus, using this new dehydrating contact agent – chromium oxide upon alumina (which possesses isomerizing properties with respect to isolated dienes, as we have shown previously [8]) enabled the total output of the two conjugated diene hydrocarbons (B and C) to be raised considerably, to 59% of the theoretical, by isomerizing the 2-methylpentadiene-1,4 (A) formed as an intermediate product. Special experiments bore out that 2-methylpentadiene-1,4 is readily isomerized above chromium oxide on alumina, producing a mixture of isomeric diene hydrocarbons with conjugated double bonds (B and C):

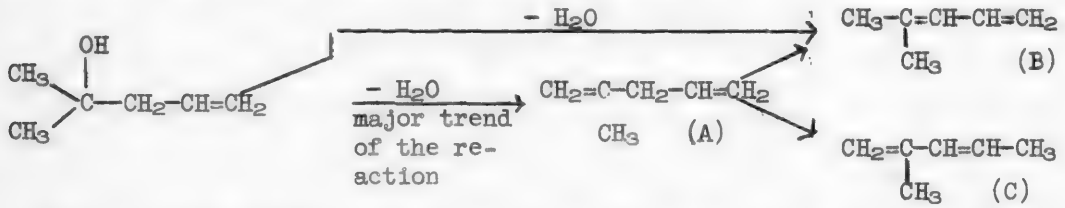


Raman spectrum analysis* of the products of catalytic dehydration of dimethylallylcarbinol and the products of the catalytic isomerization of 2-methylpentadiene-1,4 (A) indicated that the mixture of conjugated dienes prepared by dehydrating the carbinol contains approximately 40% of 2-methylpentadiene-2,4 (B), while the percentage of the latter is approximately 30% when the isolated diene (A) is isomerized.

The data of spectroscopic analysis were confirmed for the first case by determining the composition of a mixture of conjugated dienes by reacting them with maleic anhydride (the 2-methylpentadiene-2,4 constituted approximately 35%).

Hence, of the two conjugated dienes (B and C), 2-methylpentadiene-1,3 – which can be formed only as the result of the isomerization of the isolated diene: 2-methylpentadiene-1,4 (A) – predominates.

We may thus conclude that the primary product of the catalytic dehydration of dimethylallylcarbinol is, in the main, a hydrocarbon with isolated double bonds: 2-methylpentadiene-1,4 (A), which is then isomerized in two ways, giving rise to a mixture of conjugated diene hydrocarbons (B and C):



This equation confirms the correctness of the assertion made by S.N.Reformatsky cited above.

*The spectra of 2-methylpentadiene-1,4 (A) and 2-methylpentadiene-2,4 (B) have been studied for the first time.

EXPERIMENTAL

Synthesis of dimethylallylcarbinol. In the present paper we have added some refinements to the Yavorsky method of synthesizing dimethylallylcarbinol, which are of fundamental importance to the successful performance of the reaction. The synthesis of dimethylallylcarbinol is described below.

Magnesium (1 gram atom) was activated with a small quantity of allyl bromide, added at such a rate that the ester boiled even when the reaction vessel was chilled with ice water; only afterward was an ether solution of a mixture of allyl chloride (1 mol) and acetone* (1 mol) added, with the same chilling and with vigorous stirring, at such a rate as to keep the ester boiling evenly and vigorously. The evenness of the reaction is a prime condition for securing the maximum yield of the carbinol. After addition of the acetone – allyl chloride mixture was complete (within 45-50 minutes), the reaction mixture was boiled for about an hour over a water bath; it was then decomposed by pouring the reaction mixture out over ice and then adding ammonium chloride and dilute acetic or sulfuric acid. The ether layer (together with ether extracts of the aqueous layer) was washed until its reaction was neutral and then desiccated with calcined potash, the drying agent being changed three times for a fresh one (to break up the hydrate [10] of dimethylallylcarbinol). The resulting dimethylallylcarbinol had the following constants, after being distilled twice with a dephlegmator (yield: 67-70% of the theoretical):

B.p. 117-119° (758 mm); n_D^{20} 1.4279; d_4^{20} 0.8328; Literature data: b.p. 119.5°; d_0^{18} 0.8307 [10]; B.p. 118.3-118.8° [11]; B.p. 117-119°; n_D^{20} 1.4301; d_4^{20} 0.8335 [12].

Dehydration of dimethylallylcarbinol. The carbinol was passed over chromium oxide upon alumina** (tube diameter 1.5 cm, catalyst layer 60 cm long) in a current of nitrogen at various temperatures and rates of flow. The catalyst was regenerated after 30 g of the carbinol had flowed over it, yielding 22-23 g of desiccated catalyzate (about 90% of the theoretical) in each run. Distilling the catalyzate over sodium yielded a 54-78° hydrocarbon fraction, which was then fractionated over sodium into a tower containing 25 theoretical plates. Two fractions were collected:

I. 2-Methylpentadiene-1,4 (A):

B.p. 56.5° (761 mm); n_D^{20} 1.4053; d_4^{20} 0.6932; MR_D 29.06. Computed for C_6H_{10} 28.97.
Literature data: b.p. 57-58° (760 mm); n_D^{17} 1.4081; d_4^{17} 0.6960 [8]: B.p. 55.8-55.9° (750 mm); n_D^{20} 1.4050; d_4^{20} 0.6938 [13].

II. Mixture of 2-methylpentadiene-2,4 (B) and 2-methylpentadiene-1,3 (C):

B.p. 72.5-75.5° (761 mm); n_D^{20} 1.4474; MR_D 30.69, Computed for C_6H_{10} 28.97; EM_D 1.72.
Literature data for the diene mixture: B.p. 72-75.8° (766 mm) [8].

The results of our experiments on the dehydration of dimethylallylcarbinol above chromium oxide on alumina are listed in Table 1.

As Table 1 indicates, the optimum conditions for producing the diene hydrocarb- (with a b.p. of 72.5-75.5°) are: 250° temperature and 0.10-0.12 ml of the carbinol flowing past per minute. As we have shown previously [8], these are precisely the optimum conditions for the isomerization of isolated dienes into conjugated ones. Under these conditions, the yield of the mixture of conjugated dienes – 2-methylpentadiene-2,4 and 2-methylpentadiene-1,3 – is 59% of the theoretical, based on the original carbinol.

*The acetone was first purified as follows: it was mixed with an equal volume of water and then distilled from the aqueous solution, after which it was desiccated with calcium chloride and set aside to stand for a day with potassium permanganate (with periodic shaking); the next day it was boiled with the permanganate; then the acetone was distilled and again carefully desiccated by boiling it for three days with calcium chloride (changing the drying agent every 5 to 6 hours).

**The preparation of this mixed contact agent has been described in one of our previous reports [9].

TABLE 1 *

Experimental conditions		Total yield of diene hydrocarbons, % of the theoretical	Composition of hydrocarbon fraction		
Temperature, °	Rate of flow, ml/min		2-methylpentadiene-1,4, b.p. 56.5°, %	Intermediate fraction with b.p. of 56.5-72.5°, %	Mixture of 2-methylpentadiene-2,4 and 2-methylpentadiene-1,3, b.p. 72.5-75.5°, %
200	0.05-0.07	54%	51	4	45
210	0.05-0.07	70%	44	4	52
220	0.05-0.07	72%	31	5	64
240	0.10-0.12	70%	17	8	75
250	0.05-0.07	67%	11	6	83
250	0.10-0.12	70%	11	5	84
250	0.20-0.25	73%	35	4	61

Analysis showed that the mixture of conjugated diene hydrocarbons with a b.p. of 72.5-75.5° recovered by fractionation contained about 35% of 2-methylpentadiene-2,4 (B) and about 65% of 2-methylpentadiene-1,3 (C). The composition of the mixture was determined by treating it with maleic anhydride dissolved in toluene and quantitatively determining the addition product formed by one of the constituents of the mixture: 2-methylpentadiene-1,3 (C)[14]. The 2-methylpentadiene-2,4 (B), which does not react with maleic anhydride (under the conditions adopted for the reaction), possessed the following constants after distillation over sodium into a tower with 25 theoretical plates:

B.p. 76.3° (762 mm); n_D^{20} 1.4520; d_4^{20} 0.7200; MR_D 30.78, computed for C_6H_{10} 28.97; EM_D 1.81. Literature data: B.p. 76.2-76.6° (758.4 mm); n_D^{20} 1.4525; d_4^{20} 0.7189 [15]; B.p. 76.3° (760 mm); n_D^{20} 1.4505; d_4^{20} 0.7189 [14].

The dimethyltetrahydrophthalic acid secured by hydrolyzing the corresponding anhydride – the product of condensing the 2-methylpentadiene-1,3 with maleic anhydride – had a m.p. of 153-154° (the literature gives the m.p. as 154° [14]).

The quantitative composition of the mixture of conjugated dienes thus found was confirmed by a study of its Raman spectrum (vide infra).

Isomerization of 2-methylpentadiene-1,4 above chromium oxide on alumina. The 2-methylpentadiene-1,4 (22-25 g being used in each run) was passed over chromium oxide on alumina at 250° in a current of nitrogen. The polymers were removed from the catalyzate by distillation, and the resulting mixture of diene hydrocarbons with a b.p. of 56-57° was fractionated above sodium into a tower with 25 theoretical plates: two fractions were collected: the original 2-methylpentadiene-1,4 (A) with a b.p. of 56-57°, and a mixture of isomeric conjugated dienes (B and C) with a b.p. of 72.5-75°. The test results are given in Table 2.

The fraction with a b.p. of 72.5-75° (754 mm) possessed the following constants: n_D^{20} 1.4480; d_4^{20} 0.7177. Analysis of the Raman spectrum of this fraction (vide infra) indicated that its composition is the same as that of the corresponding fraction secured in the dehydration of dimethylallylcarbinol. Thus, 2-methylpentadiene-1,4 (A)

*All the figures in this table are the means of several similar tests. The carbinol was sometimes recovered in the experiments made at 200-210°; the carbinol was completely dehydrated at 220-250°, but an appreciable quantity of polymers was formed. At still higher temperatures (260-290°), the quantity of polymers increased sharply, while the output of the diene hydrocarbons dropped off.

TABLE 2

Test temperature, °	Rate of flow, ml/min	Total yield of diene hydrocarbons, % of the theoretical *	Composition of the diene fraction	
			Per cent of the original 2-methylpentadiene-1,4, b.p. 56-57°	Mixture of conjugated dienes (B) and (C), b.p. 72.5-75°, %
250	0.05-0.07	6	–	95
250	0.12-0.15	53	4-5	90
250	0.25-0.30	62	4-5	90

which has isolated double bonds, is isomerized above chromium oxide on alumina, forming a mixture of two conjugated dienes: 2-methylpentadiene-2,4 (B) and 2-methylpentadiene-1,3 (C).

Optical Investigation

The Raman spectra of preparations of 2-methylpentadiene-1,4 (A), 2-methylpentadiene-2,4 (B), and two mixtures of conjugated dienes: Mixture 1 with a b.p. of 72.5-75.5°, secured by dehydrating dimethylallylcarbinol; and Mixture 2, with a b.p. of 72.5-75°, secured by the catalytic isomerization of 2-methylpentadiene-1,4, were analyzed in a Steinheil triple glass prism spectrograph. The operational procedure, the films, and the materials used in the present research have been described previously [16,17]. The data listed for the Raman spectrum are the mean values of three to four determinations.**

The intensity of the lines was measured by taking microphotographs with the Zeiss recording microphotometer, using the method previously described [18].

The standard used for computing the intensity of the 2-methylpentadiene-1,4 and 2-methylpentadiene-2,4 lines on a single scale was chloroform; the intensity of the 669 cm^{-1} line for chloroform was taken as 197 units/mol and cm^{-1} on a scale on which the intensity of the 802 cm^{-1} line for cyclohexane was taken as 250 units/mol and cm^{-1}.

The explored sectors are listed below in Table 3.

TABLE 3

Spectrum of 2-Methylpentadiene-1,4 ***

232(6); 257 (6); 311 (5); 369 (20); 415 (6); 440-459 (8; w); 547 (4); 630 (13); 704 (10); 769 (4); 795 (0); 816-830 (23; dl, b); 889 (12); 912 (12; b); 931 (10); 1010 (5); 1040 (5); 1133 (5); 1150 (6); 1205 (22); 1240** (20); 1270 (15); 1296 (58); 1323** (20); 1414 (60); 1430 (50); 1643 (118); 1653 (110); 2998 (125); 2930 (130); 2997 (126); 3003 (100); 3088 (50).

Spectrum of 2-Methylpentadiene-2,4 ****

207 (10; w); 250 (15; w); 307 (6); 363 (60); **437** (39); 524 (25); 556 (0); 764 (6); 813 (30); 863 (8); 895 (42); 832 (6); 951 (10); 992 (18); 1067 (27); 1088 (28); 1147** (88); **1216** (270); 1293 (73); **1330** (165); 1356 (8); 1381 (55); 1418 (27); 1452 (100); 1601 (155)**; 1623 (13); 1654 (970; w); 2807 (100); 2864 (240); 2885 (272); 2922 (419; w); 2970 (220); 3012 (294); 3092 (197); 3128 (200).

* A large quantity of polymers was formed in all the runs, especially when the rate of flow of the diene was

** Possible superposition of an exciting Hg line (24,705 cm^{-1}) upon the line.

*** Width of Spectrograph slit 6 cm^{-1}.

**** The width of the spectrograph slit was 3 cm^{-1} in two instances and 6 cm^{-1} in two other instances.

Table 3 (Continued)

Spectrum of Mixture I (b.p. 72.5-75.5°) of Conjugated Diene Hydrocarbons (Products of the Dehydration of Dimethylallylcarbinol)

202 (10; w); 242-257 (25); 307 (5); 364 (54); **437** (14); 448 (20); 482 (5); 525 (33); 531 (15); 587 (0); 706 (6); 767 (5); 793 (0); 812 (28); 828 (15); 862 (14); 884 (20); 896 (24); 932 (14); 1015 (34); 1036-1042 (6; w); 1099 (8); 1117 (5); 1147 (40); 1154 (8); **1216** (113); 1240 (10); 1270 (16); 1294 (55); 1307 (75); **1330** (76); 1358 (6); 1382 (53); 1417 (25); 1452 (72); 1601 (103)* ; 1612 (82); 1642-1656 (577;w).

Spectrum of Mixture II (b.p. 72.5-75°) of conjugated Diene Hydrocarbons (Products of the Isomerization of an Isolated Diene – 2-Methylpentadiene-1,4)

200 (12; w); 257 (18; w); 364 (19); **437** (11); 448 (16); 490 (5); 525 (30); 531 (12); 586 (0); 812 (16); 828 (12); 884 (13); 896 (16); 930 (8); 963 (8); 1015 (42); 1040 (9); 1070 (9); 1085 (18); 1117 (5); 1147 (56; b); **1216** (81); 1240 (12); 1270 (10); 1293 (33); 1307 (86); **1329** (46); 1358 (10); 1382 (31); 1417 (19); 1452 (45; w); 1601 (62);** 1642-1657 (336; w).

Note: w = wide band; b = background; dl = double line; the intensity of the weak lines in the spectrum was estimated visually from a series of comparison lines measured photometrically.

The spectrum of 2-methylpentadiene-1,4 (A), which does not have a symmetrical structure and possesses a group of the $RR'C=CH_2$ and $RCH=CH_2$ types, contains frequencies that are characteristic of each of these groups individually, namely, 1653 cm^{-1} and 1643 cm^{-1} respectively. It is worthy of note that the intensity of the 1643 cm^{-1} line per mol and cm^{-1} is practically equal to the intensity of the 1642 cm^{-1} line in normal alkenes-1 [17]. The intensity of the 1653 cm^{-1} line is likewise close to that of the 1642 cm^{-1} frequency that is characteristic of alkenes-1.

The spectrum of 2-methylpentadiene-2,4 (B) – the characteristic frequency of the conjugated double bonds in the 1600 cm^{-1} region is a wide band, the center of which lies at 1654 cm^{-1}. The bifurcation of lines that we have observed in other conjugated dienes and reported in our previous paper [18] is not found in 2-methylpentadiene-2,4, the peak of the 1654 cm^{-1} line exhibiting no bifurcation in the microphotograph.

Determining the percentage of 2-methylpentadiene-2,4 (B) in Mixtures I and II was effected by measuring the relative intensities of the lines for 2-methylpentadiene-2,4 and the 669 cm^{-1} line for chloroform, a certain quantity of which was added to the mixtures. The line intensities were calculated in the same units as those used for the spectra of the pure hydrocarbons.

Several factors had to be borne in mind when determining the percentage of 2-methylpentadiene-2,4 in Mixtures I and II: the 1656 cm^{-1} line could not be used, since the other diene (2-methylpentadiene-1,3) present in each mixture, might have a line that had an adjacent frequency and was superposed on it. For the same reason we could not employ the 1452 cm^{-1}, 1417 cm^{-1}, and 1382 cm^{-1} lines, either.

The outline of the 1293 cm^{-1} line of 2-methylpentadiene-2,4 largely overlapped that of the intense 1307 cm^{-1} line present in the spectra of Mixtures I and II, and it was therefore impossible to use that line either. Similar cases of overlapping existed in the spectra of Mixtures I and II for the following pairs of lines: 896 cm^{-1} and 884 cm^{-1}, and 525 cm^{-1} and 531 cm^{-1}, the 896 cm^{-1} and 525 cm^{-1} lines belonging to 2-methylpentadiene-2,4 and the other two to the other constituent of the mixtures. The 812 cm^{-1} line was comparatively weak, and its outline varied in the

*Possible superposition of an exciting Hg line (24,705 cm^{-1}).

**Possible superposition of an exciting Hg line (22,99 cm^{-1}).

mixtures. The 364 cm^{-1} and 254 cm^{-1} lines in the spectrum of 2-methylpentadiene-2,4 and in the spectra of Mixtures 1 and 2 overlapped the 366 cm^{-1} and 261 cm^{-1} lines, respectively, of the chloroform added to the mixtures.

That is why we used only the intensive, fairly well isolated lines of 2-methylpentadiene-2,4 in determining the percentage of 2-methylpentadiene-2,4 in Mixtures I and II, as the outlines of these lines in the mixture spectra obviously were no different from their outlines in the spectrum of the pure preparation of 2-methylpentadiene-2,4, namely: the lines 1330 cm^{-1}, 1219 cm^{-1}, and 437 cm^{-1}.

The percentages of 2-methylpentadiene-2,4, as determined by means of these lines, averaged: about 41% in Mixture I and about 29% in Mixture II.

It should be noted that the optical and chemical (maleic-anhydride reaction) methods of determining the percentage of 2-methylpentadiene-2,4 in Mixture I yielded results that were quite close (about 41% and 35%).

SUMMARY

1. A method has been developed for dehydrating an unsaturated hydrocarbon – dimethylallylcarbinol – above a mixed catalyst: chromium oxide on alumina. The yield of conjugated diene hydrocarbons, products of the carbinol dehydration, is 59% of the theoretical when this method is used.

2. A study has been made of the catalytic isomerization of 2-methylpentadiene-1,4 above chromium oxide on alumina. It is shown that this gives rise to a mixture of conjugated dienes: 2-methylpentadiene-2,4 and 2-methylpentadiene-1,3.

3. The mechanism of the reaction involving the dehydration of dimethylallylcarbinol is suggested, based on the results obtained in the present research.

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SYNTHESIS OF HYDROCARBONS

XV. THE SYNTHESIS OF ALKYNES-3 (γ-ACETYLENIC HYDROCARBONS)

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During a study of the phenomenon of contact isomerization of acetylenic hydrocarbons we have worked out a method for the synthesis of γ-acetylenic hydrocarbons (alkynes-3), involving the alkylation of sodium derivatives of α-acetylenic hydrocarbons (1-sodium alkynes-1) by diethyl sulfate.

Diethyl sulfate was used as an ethylating agent only for the magnesium bromide derivatives of the α-acetylenic hydrocarbons [1,2]; the sodium derivatives were ethylated solely by ethyl p-toluenesulfonate [3].

The present paper describes the synthesis of hexyne-3, heptyne-3, octyne-3, and nonyne-3:

$$RC{\equiv}CH \xrightarrow{NaNH_2} RC{\equiv}CNa \xrightarrow{(C_2H_5)_2SO_4} RC{\equiv}C{-}C_2H_5,$$

(where R = C_2H_5, C_3H_7, n-C_4H_9 and n-C_5H_{11}).

The yields of γ-acetylenic hydrocarbons in the foregoing reaction were 50, 26, 41, and 31% of the theoretical, respectively.

The hydrocarbons prepared were analyzed by the Raman spectrum method. The presence of certain characteristic frequencies * in their Raman spectra confirmed their structure as γ-acetylenic hydrocarbons.

EXPERIMENTAL

Synthesis of alkynes-3. The original α-acetylenic hydrocarbons: butyne-1, pentyne-1, hexyne-1, and heptyne-1, produced by detaching two molecules of hydrogen bromide from the respective 1,2-dibromoalkanes (by heating the latter to 170° with sodium amide in kerosene), possessed the following constants after distillation into a tower with 16 theoretical plates**:

Pentyne-1: B.p. 39.5–40° (750 mm); n_D^{20} 1.3859; d_4^{20} 0.6931;
Hexyne-1: B.p. 71–72° (750 mm); n_D^{20} 1.3993; d_4^{20} 0.7149;
Heptyne-1: B.p. 98–99° (750 mm); n_D^{20} 1.4105; d_4^{20} 0.7354.

* The complete spectra (with precise intensities) of the synthesized alkynes-3, and of their isomeric alkynes-1 and alkynes-2, will be described in a subsequent report on research carried out jointly with P. A. Akishin.

** The butyne-1 was used in the reaction as soon as it had been prepared from 1,2-dibromobutane.

The sodium amide (using an excess of 30%), carefully pulverized under absolute ether, was placed in a three-necked flask (fitted with a reflux condenser, a dropping funnel, and a stirrer equipped with a mercury seal) and covered with a layer of absolute ether; the original α-acetylenic hydrocarbon was slowly added, with constant stirring, to the ether in the flask, which was heated to boiling.* After all the α-acetylenic hydrocarbon had been added (16 g of butyne-1, 10 g of pentyne-1, 10 g of hexyne-1, and 22 g of heptyne-1, respectively), the reaction mixture was heated for 2 to 3 hours until no more ammonia was evolved, and then the diethyl sulfate (10% excess) was added to it with constant heating and stirring. Heating was continued for 18 to 24 hours, until the ethylation reaction was wholly complete. The reaction mixture was then decomposed with water, and the ether layer, together with the ether extract of the aqueous layer, was washed with water and desiccated with calcium chloride. The ether was driven off with a meter-high dephlegmator; the residue was boiled for several hours with a 10% sodium hydroxide solution to hydrolyze the unreacted diethyl sulfate, and then the hydrocarbon mixture (the original alkyne-1 and the synthesized alkyne-3) was distilled off together with the water. The mixture was then washed with water, desiccated with calcium chloride, and fractionated into a tower with 16 theoretical plates after the high-boiling fractions had first been eliminated by distillation. The original alkyne-1 (15 to 25% by weight of what was placed in the reaction) separated out as a low boiling fraction during this distillation into the tower. The constants and yields of the synthesized alkynes-3 are given in Table 1; the data found in the literature are given in Table 2.

TABLE 1

Constants of Alkynes-3, Prepared by Alkylating 1-Sodium Alkynes-1 with Diethyl Sulfate

Alkyne-3	Boiling point, °	n_D^{20}	d_4^{20}	MR_D		Characteristic frequencies in Raman spectra	Yield, % of theory
				Found	Computed**		
Hexyne-3...	80-80.5 (767 mm)	1.4132	0.7230	28.34	28.48	2229 2246, 2300	50
Heptyne-3..	105.5-106 (758 mm)	1.4220	0.7527	32.33	32.48	2237, 2296	26
Octyne-3...	132-132.5 (765 mm)	1.4269	0.7542	37.75	37.51	2232, 2293	41
Nonyne-3...	155-155.5 (749 mm)	1.4303	0.7637	41.97	42.12	-	31

TABLE 2

Literature Data on the Alkynes-3

Alkyne-3	Boiling point, °	n_D^{20}	d_4^{20}	Reference
Hexyne-3	81.2 (747 mm)	1.4109	0.7230	[5]
Heptyne-3	106 (760 mm)	1.4230	0.765	[6]
Octyne-3	132.8 (747 mm)	1.4250	0.7529	[5]
Nonyne-3	153-155 (749 mm)	1.4299	0.7650	[2]

Analyses of the synthesized alkynes:

Hexyne-3. Found %: C 87.71; H 12.26. Computed %: C 87.72; H 12.28.
Heptyne-3. Found %: C 87.36; H 12.42. Computed %: C 87.42; H 12.58.
Octyne-3. Found %: C 87.25; H 12.70. Computed %: C 87.20; H 12.80.

*In synthesizing hexyne-3, the butyne-1 was added to the sodium amide at room temperature from a dropping funnel provided with a cooling jacket.

**The molecular refraction of the γ-acetylenic hydrocarbons was computed by a method that made no use of the constant increment for the triple bond [4].

SUMMARY

1. A method has been developed for synthesizing alkynes-3 by alkylating 1-sodium alkynes-1 with diethyl sulfate.

2. This method has been used to synthesize hexyne-3, heptyne-3, octyne-3, and nonyne-3 with yields of 50, 26, 41, and 31% of the theoretical, respectively.

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THE SYNTHESIS AND CATALYTIC TRANSFORMATIONS OF ALIPHATIC SULFIDES IN CONTACT WITH AN ALUMINOSILICATE CATALYST

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There are references in the literature to the catalytic transformations of sulfur compounds with metallic, oxide, and sulfide catalysts, but there are no papers on the catalytic transformations of sulfur compounds with an aluminosilicate catalyst. The present paper reports the results obtained in a study of the catalytic conversions of aliphatic sulfides when in contact with an aluminosilicate catalyst.

We made a study of the contact conversions of individual sulfur compounds containing the C_9 and C_{10} radicals. The resulting catalyzates also yielded individual compounds that were identified by ther respective constants. Conclusions regarding the changes occurring during catalysis were based upon the compounds found in the catalyzates.

In order to obtain comparable results, the sulfur compounds were passed over the catalyst at standard conditions whenever possible. In some cases, only the experimental temperature was changed. 30 g of the aluminosilicate catalyst was placed in the reaction tube, which was heated in an electric furnace. The experiments were of the circulating type. The sulfur compounds entered the reaction tube from a dropping funnel in a slight current of nitrogen (nitrogen flow rate: 600-800 ml per hour). The volumetric rate of flow of the substance was 0.25. The resulting catalyzates were collected in an ice-chilled receiver.

Hydrogen sulfide was evolved in every case when the sulfur compound was passed over the catalyst; the resulting catalysts were therefore washed with water until all the hydrogen sulfide had been removed (test with cadmium chloride) and then desiccated. They were then fractionated to recover the individual compounds.

The catalyst showed no apparent signs of poisoning during the decomposition of the sulfur compounds. The catalyst was regenerated after every run. Regeneration was effected by passing a current of air over the catalyst at 500° until it whitened, after which the air was forced out of the reaction tube by passing nitrogen through. Decylthiol, dinonyl sulfide, and dinonyl disulfide were subjected to catalysis, i.e. representatives of those classes of aliphatic sulfur compounds that have been found in sulfurous petroleums.

The sulfur compounds needed for this research were prepared by methods described in the literature for the synthesis of their homologs. Dinonyl sulfide, which we prepared for the first time, was synthesized (with a yield that was 59% of the theoretical) by reacting potassium sulfide with nonyl bromide. Dinonyl disulfide, which is not described in the literature, was prepared (with a yield that was

45% of the theoretical) by reacting nonyl bromide with sodium thiosulfate and then decomposing the resulting product with aqueous alkali. Decylthiol was prepared by reducing didecyl disulfide with zinc and hydrochloric acid; the yield was satisfactory: 82% of the theoretical.

The catalytic conversions of decylthiol above an aluminosilicate catalyst were investigated at 250 and 300°. Passing the decylthiol over the catalyst at 250° yielded a catalyzate that contained decene-1 (30.3% of the catalyzate by weight), didecyl sulfide (23.8% of the catalyzate by weight), and the original decylthiol (20%).

Only one product of the decomposition of decylthiol could be recovered from the 300° catalyzate, namely, decene-1 (18.6% of the catalyzate by weight); the catalyzate also contained the original decylthiol (27.4% of the catalyzate by weight). If any didecyl sulfide was formed, the quantity was so minute as to defy our attempt to recover it.

Hence, at low temperatures the conversion of decylthiol follows two paths: the formation of didecyl sulfide, with the evolution of one molecule of hydrogen sulfide from two molecules of the thiol; and the formation of decene-1, with the evolution of one molecule of hydrogen sulfide from one molecule of the thiol.

$$2C_{10}H_{21}SH \rightarrow C_{10}H_{21}-S-C_{10}H_{21} + H_2S$$

$$C_{10}H_{21}SH \rightarrow C_{10}H_{20} + H_2S.$$

At higher temperatures the only process that occurs is the formation of decene-1

P. Sabatier and A.Mailhe [1] obtained similar results in their study of the conversions of ethyl- and isoamylthiols above cadmium sulfide. They found that these thiols are converted into the corresponding sulfides at low temperatures (of the order of 300-360°), and into alkenes at higher temperatures, (360-400°).

The results we obtained with decylthiol indicate that the higher homologs of the aliphatic thiols exhibit the same pattern of behavior, even though the research was carried out with a different catalyst.

The conversion of dinonyl sulfide was investigated at 300°. The resulting catalyzate yielded the primary nonylthiol (16% of the catalyzate by weight) and nonene-1 (28% of the catalyzate by weight).

There are two conceivable ways in which these compounds may be formed.

a) The sulfide breaks down into the thiol and the alkene, the reaction involving disproportionation of the hydrogen:

$$C_9H_{19}-S-C_9H_{19} \rightarrow C_9H_{19}SH + C_9H_{18}.$$

Then some of the resulting thiol is converted into the alkene, hydrogen sulfide being evolved:

$$C_9H_{19}SH \rightarrow C_9H_{18} + H_2S.$$

b) The sulfide breaks down into two molecules of the alkene, hydrogen sulfide being evolved:

$$C_9H_{19}-S-C_9H_{19} \rightarrow H_2S + 2C_9H_{18}.$$

The thiol is formed by a secondary addition reaction of hydrogen sulfide to the resulting alkene:

$$C_9H_{18} + H_2S \rightarrow C_9H_{19}SH.$$

In order to ascertain the possibility of hydrogen sulfide being added to the alkene under our experimental conditions, we ran a special experiment: the decene preparation was passed over the aluminosilicate catalyst at 300° in a strong current of hydrogen sulfide. We found that under these conditions hydrogen sulfide is not

added to the alkene in practice. Hence, it has been shown experimentally that the second mechanism proposed for the decomposition of the sulfides has no basis in reality. There remains the first supposition, which we believe to be correct, that the sulfide breaks down into the alkene and the thiol, with disproportionation of the hydrogen. Part of the thiol that is formed is then converted into the alkene by liberating hydrogen sulfide.

The literature contains references to the mechanism of decomposing the sulfides that we propose. M.Blagodarov [2], for instance, cites the possible reactions of thermal decomposition of the sulfides and gives the decomposition of the sulfide into an alkene and a thiol among other reactions, but he does not provide experimental confirmation of this assertion. B.L.Moldavsky and Z.I.Kumari [3] conclude from their experimental data that a thiol is the primary stage in the decomposition of sulfides.

We investigated the catalytic conversion of dinonyl disulfide at 300°. The resulting catalyzate yielded the primary nonylthiol (27% of the catalyzate by weight) and a small amount of nonene-1 (3.7% of the catalyzate by weight). These results leave no room for doubt about the mechanism involved in the decomposition of the disulfide. The principal reaction is the destructive hydrogenization of dinonyl disulfide with the formation of two molecules of nonylthiol. Part of the resulting thiol is then converted into the alkene, hydrogen sulfide being evolved. The rate of hydrogenating the disulfide is so much higher than the rate of the ensuing decomposition of the thiol that nonylthiol constitutes the principal product of the conversion of dinonyl disulfide. The hydrogen needed for the hydrogenation of the disulfide is formed by cracking, which occurs above an aluminosilicate catalyst at 300°. In fact, analysis of the waste gases produced when dinonyl disulfide is passed over the catalyst indicated that they contained 29% of hydrogen.

Thus, we have ascertained the processes taking place when aliphatic sulfur compounds are passed over an aluminosilicate catalyst: reactions involving the evolution of hydrogen sulfide and reactions involving the disproportionation of hydrogen are observed, together with destructive hydrogenation. The course the reaction takes is governed by the structure of the sulfide.

EXPERIMENTAL

I. Synthesis and Catalytic Conversions of Decylthiol

Normal primary decylthiol was synthesized by the C.R.Noller and J.J.Gordon method [4], involving the reduction of didecyl disulfide by zinc and sulfuric acid. The didecyl disulfide was prepared by the method described by S.Blackburn and F.Challenger [5] for the synthesis of diamyl disulfide.

Synthesis of didecyl disulfide. The didecyl disulfide was synthesized by reacting decyl bromide with sodium thiosulfate and then treating the reaction mixture with an alkali solution:

$$2C_{10}H_{21}Br + 2Na_2S_2O_3 \longrightarrow 2C_{10}H_{21}S_2O_3Na + 2NaBr.$$

$$2C_{10}H_{21}S_2O_3Na + 2KOH \longrightarrow C_{10}H_{21}{-}S{-}S{-}C_{10}H_{21} + Na_2SO_4 + K_2SO_3 + H_2O.$$

The decyl bromide needed for this synthesis was produced by reacting decyl alcohol with bromine and red phosphorus as follows: 284 g (1.8 mol) of decyl alcohol (b.p. 231°; n_D^{20} 1.4378; d_4^{20} 0.8340) and 18.5 g (0.6 mol) of red phosphorus were placed in a round-bottomed flask fitted with a reflux condenser, a stirrer, and a dropping funnel. 144 g (0.9 mol) of bromine was added to the reaction mixture drop by drop, while the latter was stirred and gently heated over a water bath. The reaction mixture was heated over the water bath for 6 hours, after which decyl bromide was distilled with steam superheated to 140-150°. The bromide was washed

with a 50% solution of calcium chloride, desiccated with calcium chloride, and distilled in vacuum. The yield of the decyl bromide was 341 g (85.7% of the theoretical).

B.p. 97-98° (5 mm); n_D^{20} 1.4550; d_4^{20} 1.0689.
Literature data: B.p. 104-104.5° (8 mm); n_D^{20} 1.45504; d_4^{20} 1.0683 [6].

The resultant decyl bromide was employed in the synthesis of didecyl disulfide, which was performed in the apparatus described for the preparation of the decyl bromide. 115 g (0.52 mol) of decyl bromide, dissolved in 350 ml of methanol, and 260 g (1.05 mol) of sodium thiosulfate, dissolved in 400 ml of water, were placed in the flask. The mixture was heated over a water bath for 6 hours with constant stirring. The resulting yellow liquid was kept hot over the water bath while a solution of 94 g (1.68 mol) of caustic potash in 200 ml of water was added through the dropping funnel. This caused the precipitation of a white deposit of inorganic salts, while a layer of dark brown oil formed on the surface. After all the alkali had been added, the reaction mixture was heated over the water bath for another 30 minutes. Then 800 ml of water was added to the flask, which caused the entire precipitate to dissolve. After the reaction mixture had cooled, the top layer was removed, while the bottom, aqueous layer was extracted with ether. The ether extracts were combined with the bulk of the disulfide, washed with water until its reaction was neutral, and desiccated with calcium chloride. After the ether had been driven off, the didecyl disulfide was twice distilled in vacuum. The yield of didecyl disulfide was 55 g (61.1% of the theoretical).

B.p. 210-212° (7 mm); 206-207° (2 mm); n_D^{20} 1.4818; d_4^{20} 0.8894; MR_D 110.8; Computed 110.78. (The atomic refraction of disulfide sulfur is taken to be 8.11, in accordance with the figures published by T.S.Price and D.F. Twiss [7]).

S.R.Noller and J.J.Gordon [4] prepared didecyl disulfide by reacting decyl bromide with sodium sulfide and powdered sulfur, i.e., sodium disulfide. They reduced the crude didecyldisulfide to decylthiol without determining its constants.

Preparation of decylthiol. Decylthiol was prepared by reducing didecyldisulfide, as follows:

$$C_{10}H_{21}—S—S—C_{10}H_{21} + H_2(Zn + H_2SO_4) \rightarrow 2C_{10}H_{21}SH.$$

This reduction was performed in a three-necked round-bottomed flask, fitted with a mechanical stirrer and a reflux condenser. 40 g (0.12 mol) of didecyl disulfide and 190 ml of dilute sulfuric acid (1:2) were placed in the flask. The reaction mixture was heated over a water bath while, with constant stirring, 38 g (0.58 gram atom) of zinc dust was added in small batches. Then the mixture was heated with the stirrer running for 7 hours over a glycerol bath, the latter's temperature being kept at 130-150°. After the mixture had cooled the top thiol layer was separated, and the aqueous layer extracted several times with ether. The ether extracts were combined with the bulk of the thiol, and the whole was washed with water until its reaction was neutral and then desiccated with sodium sulfate. The ether was driven off, and the thiol was distilled in vacuum. The decylthiol yield was 33 g (82.1% of the theoretical).

B.p. 96° (2 mm); 103° (9 mm); n_D^{20} 1.4576; d_4^{20} 0.8414; MR_D 56.40; computed 56.07. (The atomic refraction of thiol sulfur was taken to be 7.69, in accordance with the figures published by T.S.Price and D.F. Twiss.)

Data in the literature: b.p. 125-127° (19 mm); n_D^{20} 1.4537; d_{20}^{20} 0.8410 [4].

Catalytic Conversions of Decylthiol

a) Conversion of decylthiol at 250°. 30.5 g of decylthiol was passed over an aluminosilicate catalyst at 250° under standard conditions. The resulting catalyzate weighed 27.7 g, which represented 90.8% of the substance passed through by weight. Fractionation of the catalyzate yielded 8.4 g of decene-1 (30.3% of the catalyzate by weight).

B.p. 68-69° (29 mm); n_D^{20} 1.4228; d_4^{20} 0.7416; MR_D 48.09; computed 47.91.

Literature data: B.p. 170-173°, n_D^{20} 1.4259; d_4^{20} 0.7447 [8]; B.p. 75-78° (30 mm); n_D^{25} 1.4215; d^{25} 0.743 [8]; b.p. 52° (11 mm); n_D^{20} 1.4220; d_4^{20} 0.7396 [10].

The middle fraction of the catalyzate yielded 5.7 g of the original decylthiol (20.5 % of the catalyzate by weight), with the following constants: b.p. 97-100° (6-8 mm); n_D^{20} 1.4568; d_4^{20} 0.8406; MR_D 56.42; Computed 56.07.

The upper fraction consisted of white crystals, which were pressed out on a porous plate and recrystallized from alcohol. 6.6 g of this crystalline substance was secured (23.8% of the catalyzate by weight), m.p. 25-26°. It seemed highly probable that the white crystalline substance we had isolated was didecyl sulfide. The latter was specially synthesized by us to compare its constants with those of the substance secured from the catalyzate.

The didecyl sulfide was synthesized by a method resembling the synthesis of its homologs, namely, the synthesis of diisoamyl sulfide, described by R.Wegscheider and H.Schreiner [11], and that of dioctyl sulfide, described by W.Moslinger [12]. Both of these sulfides were prepared by the authors from the respective alkyl halogenides by reacting them with an alcoholic solution of potassium sulfide.

The reaction involving the formation of didecyl sulfide was as follows:

$$2C_{10}H_{21}Br + K_2S \longrightarrow C_{10}H_{21}—S—C_{10}H_{21} + 2KBr.$$

The alcoholic solution of potassium sulfide was prepared by dissolving 23.5 g (0.42 mol) of commercial caustic potash in 84 ml of ethyl alcohol; half of this solution was saturated with hydrogen sulfide while chilled, and then both halves were poured together. The resulting solution was placed in a round-bottomed flask fitted with a dropping funnel and a reflux condenser, and then heated over a water bath to 80°. While heating continued, 46.4 g (0.21 mol) of decyl bromide was added to the solution from the dropping funnel. Soon after the reaction began, a white precipitate of KBr began to settle to the bottom of the flask. The reaction mixture was boiled over the water bath for 3 hours after the decyl bromide had been added. After the mixture had cooled, water was added to the flask to dissolve the potassium bromide. White crystals formed on the surface of the liquid. They were taken up with ether; the ether extract was washed with water and desiccated with calcium chloride. Driving off the ether yielded 28.6 g of solid didecyl sulfide. The substance was purified by recrystallizing it from ethyl alcohol and then distilling it in vacuum. The yield of pure didecyl sulfide was 19 g (58.5% of the theoretical). B.p. 216-217° (8 mm). M.p. 25-26°.

3.910 mg substance: 10.970 mg CO_2; 4.650 mg H_2O. 4.420 mg substance: 12.430 mg CO_2; 5.225 mg H_2O. Found %: C 76.52, 76.70; H 13.31, 13.23. $C_{20}H_{42}S$. Computed %: C 76.35; H 13.46.

Didecyl sulfide has not been described in the literature. The melting point of the synthetic dedecyl sulfide was the same as that of the crystals secured in the catalysis of decylthiol; a mixed test sample of both substances exhibited no depression; this proved that the two substances were identical. Hence, when decylthiol

was passed over a catalyst at 250°, didecyl sulfide was formed as well as decene.

b) Conversion of decylthiol at 300°. 23 g of decylthiol was passed over the aluminosilicate catalyst at 300° under standard conditions. The catalyzate weighed 19.3 g, or 83.9% of the substance passed through by weight. Fractionation of the catalyzate yielded two substances: a) 3.6 g of decene-1 (18.6% of the catalyzate by weight) with the following constants: B.p. 75-77° (32 mm); n_D^{20} 1.4208; d_4^{20} 0.7483, and b) 5.3 g of the original decylthiol (27.4% of the catalyzate by weight) with the following constants: b.p. 105.5-106.5° (9 mm); n_D^{20} 1.4568; d_4^{20} 0.8406; MR_D 56.42; computed 56.07.

When the upper fraction was cooled, crystals settled out, but we were unable to secure them in the pure state. Hence, if didecyl sulfide is formed at 300°, the quantity is so minute that it is impossible to identify it.

II. Synthesis and Catalytic Conversions of Dinonyl Sulfide

Dinonyl sulfide was synthesized by the method described above for the preparation of didecyl sulfide, namely, by reacting nonyl bromide with potassium sulfide.

Preparation of dinonyl sulfide. The raw material used to synthesize dinonyl sulfide was nonyl bromide. The nonyl bromide was prepared from nonyl alcohol by reacting the latter with bromine and red phosphorus as has been described earlier in the preparation of decyl bromide. 300 g (2.09 mol) of nonyl alcohol (b.p. 214°; n_D^{16} 1.4340; d_4^{20} 0.8364); 20.5 g (0.7 mol) of red phosphorus, and 167.6 g (2.1 mol) of bromine were used for the reaction. The yield of nonyl bromide was 225 g (52.2% of the theoretical).

B.p. 115-116° (20 mm); n_D^{20} 1.4498; d_4^{20} 1.0394.
Literature data: b.p. 88° (4 mm); n_D^{20} 1.4533; d_{20}^{20} 1.0183 [13].

Dinonyl sulfide was prepared from the nonyl bromide by the method described for the preparation of didecyl sulfide. We used 103 g (0.5 mol) of nonyl bromide, 70 g (1.25 mol) of caustic potash, and 275 ml of ethyl alcohol for the reaction. The yield of dinonyl sulfide was 42 g (59% of the theoretical). The preparation has not been described in the literature.

B.p. 185-186° (5 mm); n_D^{20} 1.4640; d_4^{20} 0.8455; MR_D 93.4; computed 93.3 (Atomic refraction for sulfide sulfur is taken to be 7.97, in accordance with the figures published by T.S.Price and D.F.Twiss [7]).

5.840 mg substance: 16.211 mg CO_2; 5.740 mg H_2O. 6.173 mg substance: 17.106 mg CO_2; 5.950 mg H_2O. Found %: C 75.71, 75.57; H 13.78, 13.58. $C_{18}H_{38}S$. Computed: C 75.44; H 13.37.

Catalytic Conversions of Dinonyl Sulfide

35 g of dinonyl sulfide was passed over an aluminosilicate catalyst at 300° under standard conditions. The resulting catalyzate weighed 31 g, or 88% by weight of the initial substance. Fractionation of the catalyzate yielded 8.7 g (28% of the catalyzate by weight) of a nonene fraction – b.p. 140-150° (at atmospheric pressure); n_D^{20} 1.4198, and 5 g (16% of the catalyzate by weight) of a 95-99° (11 mm) fraction; n_D^{20} 1.4568. Pure nonene-1 was recovered from the nonene fraction by distillation over sodium.

B.p. 144-146°; n_D^{20} 1.4170; d_4^{20} 0.7312; MR_D 43.33; computed 43.29.
Literature data: B.p. 146°; n_D^{20} 1.4161; d_4^{20} 0.7308 [14]; b.p. 33.5° (11 mm); n_D^{20} 1.4169; d_4^{20} 0.7296 [10].

Redistillation of the 95-99° (11 mm) fraction yielded normal primary nonylthiol:

B.p. 95-96° (11 mm); n_D^{20} 1.4560; d_4^{20} 0.8425; MR_D 51.62; computed 51.45.

8.239 mg substance: 20.492 mg CO_2; 9.017 mg H_2O. Found %: C 67.83; H 12.25. $C_9H_{20}S$. Computed %: C 67.42; H 12.57.
Literature data: B.p. 100-104° (20 mm); n_D^{20} 1.45197; d_{20}^{20} 0.8386 [4].

A special experiment was run to ascertain the mechanism of the decomposition of aliphatic sulfides, involving a determination of the feasibility of adding hydrogen sulfide to an alkene under our experimental conditions. This was done by passing 82 g of decene-1, with the constants: b.p. 68-69° (29 mm); n_D^{20} 1.4228; d_4^{20} 0.7416, over the aluminosilicate catalyst at 300° in a strong current of hydrogen sulfide. This yielded 5.1 g of a catalyzate, constituting 6.2% of the original substance by weight. The catalyzate yielded 1.6 g of unchanged decene-1 (31.3% of the catalyzate by weight); b.p. 69-70° (28-29 mm); n_D^{20} 1.4212. The upper fraction exhibited a thiol reaction, we were able to recover only a small quantity 0.3 g) of a substance having a n_D^{20} 1.4590 from it, however. This was evidently decylthiol, which has a refractive index of n_D^{20} 1.4570.

Hence, under our experimental conditions practically no hydrogen sulfide is added to the alkene.

III. Synthesis and Catalytic Conversions of Dinonyl Disulfide

Synthesis of dinonyl disulfide. The dinonyl disulfide was synthesized by the method described above for the preparation of didecyl disulfide, involving the reaction of nonyl bromide with sodium thiosulfate and treatment of the reaction mass with an alkali solution. 124.2 g (0.6 mol) of nonyl bromide, dissolved in 350 ml of methanol, and 300 g (1.2 mol) of sodium thiosulfate, dissolved in 375 ml of water, were used in the reaction. The reaction mixture was treated with 94 g (1.68 mol) of caustic potash, dissolved in 200 ml of water. The yield of dinonyl disulfide was 42.2 g (44.2% of the theoretical).

B.p. 211-212° (6 mm); n_D^{20} 1.4832; d_4^{20} 0.8922; MR_D 101.77; computed 101.54.

5.240 mg substance: 13.04 mg CO_2; 5.74 mg H_2O. 5.465 mg substance: 13.60 mg CO_2; 5.95 mg H_2O. Found %: C 67.88, 67.88; H 12.26, 12.18. $C_{18}H_{38}S_2$. Computed %: C 67.85; H 12.02.

Catalytic Conversions of Dinonyl Disulfide

11 g of dinonyl disulfide was passed over an aluminosilicate catalyst under standard conditions at 300°. The resulting catalyzate weighed 8 g, representing 72.7% of the original substance by weight. Fractionation of the catalyzate yielded a slight quantity of nonene-1. It weighed 0.3 g, or 3.7% by weight of the catalyzate; n_D^{20} 1.4190. Catalysis of the dinonyl sulfide (vide supra) yielded a nonene with a n_D^{20} 1.4170.

The other substance isolated from the catalyzate was nonylthiol. It weighed 2.2 g (27.5% by weight of the catalyzate).

B.p. 95-96° (11 mm); n_D^{20} 1.4560; d_4^{20} 0.8434; MR_D 51.57: Computed 51.45.

The constants of the synthesized nonylthiol are in good agreement with the constants of the nonylthiol prepared by catalyzing dinonyl sulfide and with the data in the literature (vide supra). The analysis of the waste gases was as follows: CO_2 0.2%; unsaturated compounds 1.55%; O_2 4.8%; CO 0.4% H_2 29%.

SUMMARY

1. C_9 and C_{10} aliphatic sulfides may be prepared from the corresponding bromides by reacting the latter with potassium sulfide. The sulfide yield is 50 to 60% of the theoretical.

2. C_8 and C_{10} aliphatic disulfides may be prepared from the corresponding bromides by reacting the latter with sodium thiosulfate and treating the resulting reaction mixture with an aqueous solution of an alkali. The disulfide yield is 45 to 60% of the theoretical.

3. A C_{10} aliphatic thiol can be prepared from the corresponding disulfide by reducing the latter with zinc and sulfuric acid, the yield being 80% of the theoretical.

4. Two processes take place when aliphatic thiols (decylthiol) are passed over an aluminosilicate catalyst at 250°: a) one molecule of hydrogen sulfide is evolved per two molecules of the thiol, yielding the sulfide (didecyl sulfide); b) hydrogen sulfide is evolved from one molecule of the thiol, yielding an alkene (decene-1). The latter process takes place at 300°.

5. When aliphatic sulfides (dinonyl sulfide) are passed over an aluminosilicate catalyst at 300°, the sulfide molecule is broken down, and the hydrogen is disproportionated, yielding an alkene (nonene-1) and a thiol (nonylthiol).

When aliphatic disulfides (dinonyl disulfide) are passed over an aluminosilicate catalyst at 300°, the disulfide is destructively hydrogenated, yielding a thiol (nonylthiol). Part of the resulting thiol (nonylthiol) is then converted into an alkene (nonene-1).

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THE ISOMERIZATION OF POLYMETHYLENE HYDROCARBONS WITH ALUMINUM CHLORIDE

XVI. THE ISOMERIZATION OF 1,1-DIMETHYLCYCLOPENTANE

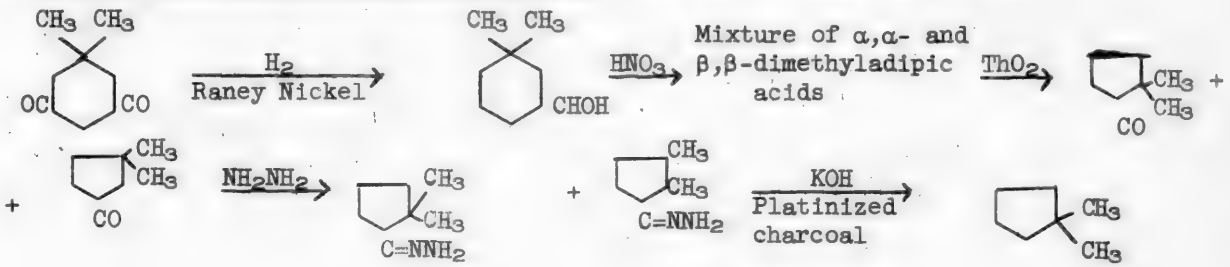
M. B. Turova-Polyak, V. A. Adamova and E. G. Treshchova

Previous observations made by one of the present authors [1] have shown that the homologs of cyclopentane that contain a tertiary carbon atom within the ring are isomerized by aluminum chloride to the corresponding methylated derivates of cyclohexane. In some instances this reaction takes place easily, without any preheating of the reaction mixture (ethyl- and propylcyclopentanes and, in part, butylcyclopentane). But as yet we do not know whether it is possible to isomerize cyclopentane hydrocarbons containing a quaternary carbon atom in the ring. This problem also deserves attention because polymethylene hydrocarbons whose rings contain a quaternary carbon atom exhibit certain peculiarities of behavior in other reactions. The research of B.A.Kazansky and his associates, for instance, has shown that the behavior of 1,1-dimethylcyclopentane during hydrogenolysis [2] is somewhat different from that of the other homologs of cyclopentane, especially from that of methylcyclopentane. 1,1-dimethylcyclohexane also exhibits singular behavior during dehydrogenation [3].

To settle this question we subjected 1,1-dimethylcyclopentane to the action of aluminum chloride. Our research indicated that 1,1-dimethylcyclopentane undergoes no change when mixed with aluminum chloride at room temperature. It is isomerized only after being heated to 100-115° for 10 to 15 hours. Under these conditions 92-95% of it is isomerized to methylcyclohexane. Thus, the presence of a quaternary carbon atom in the 1,1-dimethylcyclopentane molecule is no obstacle to the latter's isomerization into a cyclohexane hydrocarbon.

EXPERIMENTAL

Synthesis of 1,1-dimethylcyclopentane. This was effected as follows:



The raw material for the synthesis of 1,1-dimethylcyclopentane was dimedon (5,5-dimethylcyclohexanedione-1,3), with a m.p. of 148-149°. Many authors have synthesized 1,1-dimethylcyclopentane from dimedon; the highest yield, however, was achieved in the research by B.A.Kazansky, Z.A.Rumyantseva, and M.I.Batuev [2]. We employed the procedure set forth in this latter paper, making some changes in the conditions for the initial stage of the synthesis because we were unable to obtain 3,3-dimethylcyclopentanol-1 with a yield of 64-68% by following the specified procedure faithfully. Only after we had changed the pressure and the temperature were we able to obtain a yield of 68-69% of the alcohol. This was done by placing a solution of 85 g of dimedon in 1 liter of 95% ethyl alcohol in a 2.5 liter rotary autoclave and adding 17 g (20%) of wet Raney nickel [4]. At an initial hydrogen pressure of 90 atm the autoclave was heated to 160° for 1 hour; the pressure gradually rose from 90 to 105 atm. Then the temperature of 160° was maintained for another hour; during this period the pressure dropped to 97 atm. The autoclave was then cooled to room temperature. This was accompanied by a gradual drop of the pressure to 65 atm. Hydrogen was then pumped in again until the pressure reached 90 atm, and the autoclave was heated to 200° for 1.5 hours, causing the pressure to rise to 150 atm. The temperature of 200° was maintained for 5 to 6 hours, during which time the pressure gradually dropped to 130 atm. This completed the hydrogenation process. As soon as the temperature within the autoclave dropped to room temperature, the pressure dropped to 70 atm. Then the catalyst was filtered out of the reaction mixture, the alcohol was distilled with a dephlegmator, and the 1,1-dimethylcyclohexanol-3 was distilled in vacuum. The 1,1-dimethylcyclohexanol-3 (68.8% yield) possessed the following constants: b.p. 99° at 35 mm; d_4^{18} 0.8930; n_D^{18} 1.4562; MR_D 38.87; computed 38.34.

The resulting alcohol was oxidized with dilute nitric acid and ammonium metavanadate, by the N.D.Zelinsky and N.V.Elagina method [5]. The yield of the mixture of α,α- and β,β-dimethyladipic acids was 70%. Distilling the resulting acid mixture with 2% thorium hydroxide yielded a mixture of α,α- and β,β-dimethyl cyclopentanones, with a yield of 66%. The ketone mixture had the following constants: b.p. 151-152° at 757 mm; d_4^{20} 0.8970; n_D^{20} 1.4346; MR_D 32.55; computed 32.40. Boiling the ketone mixture with an alcoholic solution of hydrazine hydrate (0.43 mol of ketone and 0.6 mol of hydrazine hydrate in 100 ml of 95% ethyl alcohol) yielded a mixture of the hydrazones of the α,α- and β,β-dimethyl cylcopentanones. The yield of hydrazones, desiccated above fused alkali, was 97%. A mixture of the desiccated (but not distilled) hydrazones was used in synthesizing the 1,1-dimethylcyclopentane. The hydrazones were decomposed by the Kizhner method [6]. This involved boiling the mixture of hydrazones over an oil bath with caustic potash that had been fused in a silver crucible* until it turned nearly black and with pieces of platinized charcoal. The hydrocarbon was driven off over an oil bath at an oil temperature of 130-160° and a vapor temperature of 87-88°. The resulting 1,1-dimethylcyclopentane was washed with a 50% acetic acid solution, a 50% sulfuric acid solution, water, a 25% alkali solution, and again with water, then desiccated above calcium chloride and distilled above metallic sodium. The yield of 1,1-dimethylcyclopentane was 68-69%, in terms of the hydrazone, or 22.3%, in terms of the original dimedon. Its constants were as follows: b.p. 88.2° at 764 mm; n_D^{20} 1.4141; d_4^{20} 0.7546; MR_D 32.46; computed 32.22. According to B.A.Kazansky [2]: b.p. 87.25° at 751 mm; n_D^{20} 1.4133; d_4^{20} 0.7548; MR_D 32.41. Some of the 1,1-dimethylcyclopentane was brominated exhaustively with aluminum bromide. This resulted in the formation of a brown, gummous mass, which did not crystallize during the course of several months. The Raman spectrum of 1,1-dimethylcyclopentane was also analyzed. The results are given in Table 3. The principal lines of the spectrum of 1,1-dimethylcyclopentane, as found by us in the present research, coincide with the corresponding figures for the spectrum of 1,1-dimethylcyclopentane given by Batuev [2] and

*The trace of silver catalyzes the decomposition of the hydrazones to hydrocarbons.

Bakulin [7]. The spectra were secured with a Steinheil triple glass-prism spectrograph. The linear dispersion of the spectrograph was approximately 0.017 mm/cm^{-1} in the 22,938-20,336 cm^{-1} range, the width of the spectrograph slit being 0.1 mm, or 6 cm^{-1} in the spectrum. The frequencies were measured by linear interpolation from the two closest lines of the standard iron spectrum, photographed in succession by means of a Hartmann diaphragm. The intensity of the spectrum lines was estimated visually on an arbitrary scale, on which the intensity in the 1400 cm^{-1} region was taken as 10 units.

Isomerization of 1,1-dimethylcyclopentane with aluminum chloride. a) Isomerization of the hydrocarbon without heating. The reaction was carried out in the apparatus used by us in our previous researches [1]. The ratio of the freshly sublimed aluminum chloride to the hydrocarbon was 1:3. When the latter was added to the aluminum chloride, the reaction mixture did not warm up. The reaction mixture was agitated for 6 hours and then set aside to stand at room temperature for another 12 hours. The constants of the reaction product, after suitable purification, did not differ from those of the 1,1-dimethylcyclopentane originally taken for the reaction. The Raman spectrum analysis, however, indicated that the reaction product contained a trace of methylcyclohexane [769 (1.5) and 845 (0.3) lines] amounting to about 5% (Table 3).

b) Isomerization with heating. A mixture of 1,1-dimethylcyclopentane and aluminum chloride was heated for 14 hours over an oil bath, the oil temperature being 100-115°. No gaseous products were evolved during this heating. When the reaction was over, the reaction product was decanted from the aluminum chloride, suitably purified, dried, thoroughly boiled, and distilled with metallic sodium from a Favorsky flask into a tall dephlegmator. This yielded 80% of a hydrocarbon with the following constants: b.p. 98-101° at 760 mm; n_D^{20} 1.4217; d_4^{20} 0.7675; MR_D 32.44; computed 32.22. We might have expected that this isomerization would produce methylcyclohexane. Comparison of the constants of 1,1-dimethylcyclopentane, the constants of the isomerization product, and the constants of methylcyclohexane (Table 1) indicates that the bulk of the isomerization product consisted of methylcyclohexane.

TABLE 1

Constants \ Hydrocarbon	1,1-dimethylcyclopentane	Isomerization product	Methylcyclohexane [8]
B.p.	88.2° (764 mm)	98-101° (764 mm)	100.8° (760 mm)
n_D^{20}	1.4141	1.4217	1.4233
d_4^{20}	0.7546	0.7675	0.7693

This was confirmed by brominating a small quantity of the hydrocarbon (the reaction product) in the presence of aluminum bromide. Bromination yielded pentabromotoluene, with a m.p. of 282.5-288°. Another part of the isomerization product was dehydrogenated over platinized charcoal, prepared as specified by Zelinsky and Turova-Polyak [9]. The resulting catalyzate had a n_D^{20} 1.4870 and d_4^{20} 0.8522. 92-93% of aromatic hydrocarbons (toluene) were removed by the sulfuric acid method. Thus, the bromination and dehydrogenation reactions proved that the products of reaction of aluminum chloride with 1,1-dimethylcyclopentane contained methylcyclohexane. The percentage of methylcyclohexane in our reaction product was determined by making a precise fractionation, as well as a Raman spectrum analysis, of the latter. Fractionation was performed with a tower with an efficiency of 35 theoretical plates. The fractionation results are given in Table 2 and Fig. 1.

TABLE 2

Fraction No.	B.p. at 760 mm	Yield, in % of the isomerization product	Properties	
			n_D^{20}	d_4^{20}
1	89-100	12.2	1.4162	0.7587
2	100	86.1	1.4229	0.7687
3	Losses	1.7	–	–

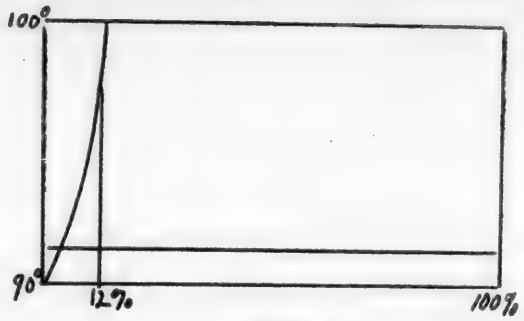


Fig. 1

TABLE 3

Spectrum of 1,1-dimethylcyclopentane, prepared in the present research	Spectrum of the reaction product, produced at room temperature	Spectrum of the reaction product, prepared with heating	Spectrum of methylcyclohexane [8]
245 (0.5); 261 (0.5); 295 (1;w); 350 (5); 397-409(1.6;b); 501 (0.5); 560(8); 718-728(2;w); 806(1.3); 830(0.8); 884-889 (10;b); 909(0.9); 938 (1.8); 956(1.8); 978-982(1.5;w); 1032(4; w); 1060(2.5); 1095 (1.2;b); 1149(1;b); 1188(1.5;b); 1227 (4.5;w); 1270(1.3); 1305(1.5); 1443(10); 1460(5); 2875(2); 2899(2); 2949(1.5;w).	242-254 (0.5; w) 299 (1;w); 350(4.5); 401-409(1;w); 444(0.3); 460(0.1); 509 (0.8); 547(0.3); 560(10); 585(0.2); 671(0.2); 729(2.5;w); 750(0.1); 769(1.5); 806(1.8;w); 830(0.7); 845(0.3); 884(12;w); 912(0.2); 938(1.4); 956(1.3); 976(0.5); 1033(4); 1060(2.5); 1097(1); 1144-1165(1;w); 1193 (0.5); 1227(5;w); 1241(0.5); 1270(1); 1305(1.5); 1323 (0.8); 1346(0.5); 1359(0.5); 1382(1); 1442(10); 1460(7).	307 (0.5); 345 (0.3); 406(4); 446(5.5); 483 (0.3); 546(5.5); 586 (0); 754(1); 769(30); 782(0); 808(0); 845 (6); 884(0.3); 912 (0.5); 943(0); 972 (6); 1034(10); 1056 (1); 1087(6;w); 1105 (0.5); 1147 (0); 1164 (7); 1204(2.5); 1227 (0.3); 1248(3.5) 1266 (7); 1305(3;w); 1346 (6;w); 1360(0.5;w); 1443(9;w); 1460(10); 2819(1); 2864(10;w).	312 (0;w); 340 (0;w) 408(14); 446(23); 522(0); 546 (21); 754(0);770(99;s); 787(0); 845(18;s); 974(16); 1004(0); 1033(31); 1061(2); 1089(13;w;dl); 1164 (14); 1205(8); 1250 (20); 1266 (23); 1306(11); 1344(16; dl);1365(2;w);1443 (34); 1460(35); 2664 (4;w);2720(2); 2844 (240); 2856(240); 2874(100); 2894(100) 2919(270); 2935(290); 2955(100;w).

Table 2 indicates that the constants of Fraction 2 are those of methylcyclohexane (Table 1). Fraction 1 is a mixture of the unreacted 1,1-dimethylcyclopentane and the methylcyclohexane. The percentage of 1,1-dimethylcyclopentane in this fraction was computed from the specific volumes of methylcyclohexane (1.2998), 1,1-dimethylcyclopentane (1.3252), and Fraction 1 (1.3180). We found that approximately 70% of Fraction 1 consisted of unreacted 1,1-dimethylcyclopentane, representing 8-9% of the total isomerization product. Thus, the action of aluminum chloride upon 1,1-dimethylcyclopentane isomerizes 91-92% of the latter to methylcyclohexane, with the ring being enlarged. The Raman spectrum of the isomerization product, together with the spectra of 1,1-dimethylcyclopentane and methylcyclohexane, is given in Table 3.

Comparison of the spectrum of the isomerization product with those of methylcyclohexane and 1,1-dimethylcyclopentane indicates that most of the hydrocarbon mixt

we had produced consisted of methylcyclohexane. The intensity of the spectrum lines was measured visually, while the true intensity of the (100%) pure 1,1-dimethylcyclopentane lines was adopted, for calculation, from an analogy with the other isomers of dimethylcyclopentane (ca.35-30 units). The percentage of 1,1-dimethylcyclopentane was determined from the 884(0.3) spectrum line, while that of methylcyclohexane was determined from the 769(30); and 845(6) lines. Our calculations indicated that most of our reaction product consisted of methylcyclohexane (95-97%), with a trace of unreacted 1,1-dimethylcyclopentane not exceeding 5%.

After this research was completed, P.A.Bazhulin [7] published a paper that contains the Raman spectrum of 1,1-dimethylcyclopentane with the line intensities measured photometrically. The frequencies of the 1,1-dimethylcyclopentane spectrum measured by us are practically identical with Bazhulin's spectrum frequencies. Using the line intensities in the Raman spectrum of 1,1-dimethylcyclopentane as measured photometrically by Bazhulin, we recomputed the concentration of the 1,1-dimethylcyclopentane that had not been isomerized and got a figure close to 3%. This result is in good agreement with the results of our computations based upon a visual estimate of the intensities, the intensity of the 884 cm^{-1} line of 1,1-dimethylcyclopentane being taken as 30-35 units, by analogy with other isomers of dimethylcyclopentane.

SUMMARY

1. 1,1-Dimethylcyclopentane remains unchanged when mixed with aluminum chloride at room temperature.

2. When 1,1-dimethylcyclopentane is heated with aluminum chloride to 100-115° for 10 to 15 hours, it is converted into methylcyclohexane: 95-97% of it being converted according to Raman spectrum analyses, and 92% being converted according to fractionation data.

3. The presence of a quaternary carbon atom in the molecule of 1,1-dimethylcyclopentane does not interfere with its isomerization to a cyclohexane hydrocarbon.

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XXIX. THE BEHAVIOR OF FURAN AND FURANIDINE WITH METAL SULFIDES AND AMIDES

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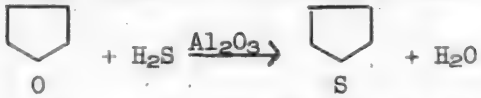
One of the ways of preparing thiophene involves passing acetylene over pyrites heated to 280-310° [1]. Endeavors have been made up to recently to improve this method (which has been pretty much supplemented by two other methods – condensing acetylene with hydrogen sulfide in the presence of alumina [2] and, especially, converting furan into thiophene catalytically [3]) by stirring the pyrites, [4]. This method may be considered to be a variant of the pyrogenic reaction for producing thiophene by passing acetylene over boiling sulfur [5], thus differing from the other two, which are catalytic methods. As we know, furan is converted into thiophene by the action of hydrogen sulfide only in the presence of an extremely vigorous dehydrating catalyst – alumina, as for the production of thiophene by condensing acetylene with hydrogen sulfide in the presence of alumina, this reaction must also pass through a stage in which not only acetaldehyde is formed, but furan as well, which is then converted into thiophene, as one of the present authors has pointed out previously [3].

The present paper deals with a study of the feasibility of preparing thiophene and thiophane noncatalytically, by means of a reaction similar to that involving acetylene and pyrites, namely, by reacting furan and furanidine (tetrahydrofuran), respectively, with metal sulfides – iron disulfide (pyrites) and the readily hydrolyzed aluminum sulfide.

It was found that no heterocyclic compounds containing sulfur are formed at all when furan and furanidine are passed over these sulfides in the temperature range of 350-600°. Under these conditions, part of the original heterocyclic compounds containing oxygen was decomposed, while part was recovered from the reaction unchanged. When a mixture of furanidine and water was passed over the aluminum sulfide, the furanidine was converted into thiophene, as might have been expected: the hydrogen sulfide evolved during the hydrolysis of the aluminum sulfide reacted normally with the furanidine when in contact with the resulting alumina, the resulting thiophane yield being 32% of the theoretical:

$$Al_2S_3 + 3H_2O \longrightarrow Al_2O_3 + 3H_2S$$



It is worthy of note that the optimum temperature for this reaction between furanidine and hydrogen sulfide at the moment of the latter's evolution (300°) is one hundred degrees below the temperature at which the highest yield is obtained in the conversion of furanidine into thiophane by reacting the former with hydrogen sulfide in the presence of alumina [6].

An attempt to substitute an imino group for the oxygen atom by letting magnesium amide act upon furan and furanidine resulted in the recovery of nothing but minute traces of pyrrole and pyrrolidine, respectively.

Thus, the results obtained in the present research reaffirm the fact that heterocyclic compounds containing oxygen can be converted into rings with other hetero atoms only by the use of vigorous dehydration catalysts.

EXPERIMENTAL

The iron disulfide (pyrites) or the aluminum sulfide, in the form of small pieces, was arranged in a layer 60 cm long in a tube with an inside diameter of 18 mm. The magnesium amide, prepared by the A.P.Terentyev method [7] from fine magnesium shavings, was arranged in a 60-cm layer within a tube with an inside diameter of 18 mm. The results obtained in the present research are listed in Tables 1, 2, and 3.

TABLE 1

Reaction of Furan and Furanidine with Iron Disulfide and Aluminum Sulfide

Test No.	Metal sulfides	Temperature	Original substance		Rate of feed, drops/minute	Composition of resulting catalyzate			Qualitative reaction for heterocyclic compounds containing sulfur
			Name	Quantity, g		Unchanged original substance recovered			
						Quantity		Boiling point	
						g	% of amt. used for reaction		
1	Pyrites	325°	Furan	5.0	6	3.4	68%	30.5-31°	
2	(FeS_2)	350	"	5.0	6	3.0	60	30-31	
3	"	400	"	5.0	6	2.7	54	30.5-32	
4	"	325	Furanidine	5.0	8	4.6	92	64-65	
5	"	350	"	5.0	8	4.3	86	64-65	
6	"	400	"	5.0	8	4.1	82	64-65.5	
7	FeS	450	Furan	10	6	4.5	45	31	Negative
8	Al_2S_3	350	"	5	6	2.6	52	30.6-31	
9	"	385	"	5	6	2.4	48	30.5-31	
10	"	410	"	5	6	2.2	44	31	
11	"	450	"	5	6	2.2	44	30.6	
12	"	500	"	5	6	2.2	44	31	
13	"	550	"	5	6	1.8	36	31	
14	"	600	"	5	6	1.6	32	31	
15	"	400	Furanidine	5	8	1.4	28	64-65	

All the thiophane recovered in the various tests was combined together and redistilled with sodium; its constants were then the same as those cited by us earlier [8]: B.p. 119-120° (758 mm); n_D^{20} 1.5050; d_4^{20} 0.9960.

The negligible amount of residue of the catalyzate distillation obtained in Tests 20 and 21 exhibited a positive pyrrole reaction (with pine shavings moistened with concentrated sulfuric acid); the residue of Test 21 had the odor of pyrrolidine, but we were unable to secure the picrate, since adding an ether solution to picric acid merely caused a slight turbidity.

TABLE 2

Reaction of a Furanidine-Water Mixture with Aluminum Sulfide

Test No.	Temperature	Quantity of furanidine, g	Quantity of water g	Rate of feed, drops/min.	Composition of catalyzate					
					Unchanged furanidine		Crude thiophene			
					g	% of amount used for reaction	g	% of theoretical	Boiling point	n_D^{20}
16	250°	5.5	10	8-10	1.2	22	3-4 drops	–	112-120°	1.4754
17	300	5.5	10	8-10	none	–	2.2	32.5	116-120	1.5000
18	350	5.5	10	8-10	none	–	1.75	30.5	116-120	1.5005
19	400	5.5	10	8-18	none	–	1.2	17.5	116-119.5	1.4822

TABLE 3

Reaction of Furan and Furanidine with Magnesium Amide

Test No.	Temperature	Original substance	Quantity, g	Rate of feed, drops/minute	Composition of catalyzate				
					Unchanged original substance			Distillation residue	
					g	% of amount used for reaction	Boiling point	Quantity	Pyrrole reaction
20	450°	Furan	11	4-5	6	54	31.2-31.5°	Negligible	Positive
21	400	Furanidine	10	8-9	3	30	64-65	Negligible	Positive

SUMMARY

1. When furan and furanidine are brought into contact with metal sulfides or amides at high temperatures, their oxygen is not replaced by sulfur or an imino group.

2. When a mixture of furanidine and water is treated with aluminum sulfide at 300-400°, it produces thiophane, with a yield that is as much as 32.5% of the theoretical.

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XXX. REACTION OF METHYL PYROMUCATE WITH ANILINE

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The ease with which the ring oxygen atom in heterocyclic compounds containing oxygen is replaced by an imino group is a function of the stability of the rings. The stability of these ring compounds depends not only upon the number of atoms in the ring, their nature, and the nature of the bonds between them, but also upon the nature of the atoms or groups linked to them. Substituting a hydroxyl or alkoxyl group or an oxygen atom for the hydrogen atoms linked to the carbon atoms in the ring greatly weakens the bonds of the bridge oxygen in the ring and facilitates its replacement. Substituting an imino group for the bridge oxygen takes place quite readily and under mild conditions [1] in γ-pyrone and its derivatives, in the lactones of unsaturated hydroxy acids and their derivatives (α-pyrones), in many lactones of saturated hydroxy acids and their derivatives, and in cyclic anhydrides: with no catalysts present, by simply evaporating with ammonia, by boiling with aqueous ammonia, and by heating with aqueous or alcoholic ammonia in sealed tubes. But even in those compounds in which the hydrogen atoms attached to the ring are replaced by an oxymethyl, carbonyl, or carbalkoxy group, the substitution of an imino group for the ring oxygen should take place (and in the instances described in the literature does take place) with greater ease than in heterocyclic compounds having no functional groups.

The present paper represents a study of the reaction of methyl pyromucate with aniline in the presence of alumina at various temperatures. It was found that pyromucanilide is formed at 190, 220, 250, and 300°, with traces of pyrrole compounds, detectable only by a qualitative reaction. At 350, 400, and 475° N-phenylpyrrole (rather than N-phenyl-α-carbomethoxypyrrole) is formed, with a yield of as much as 35% of the theoretical (at 400°), carbon dioxide being evolved abundantly and furan being formed.

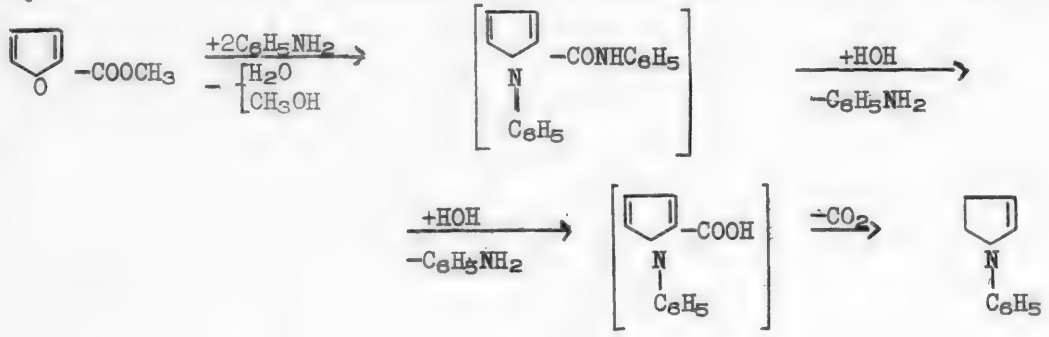
Hence, in the 190-300° interval a substituted acid amide is formed from the ester of the acid:

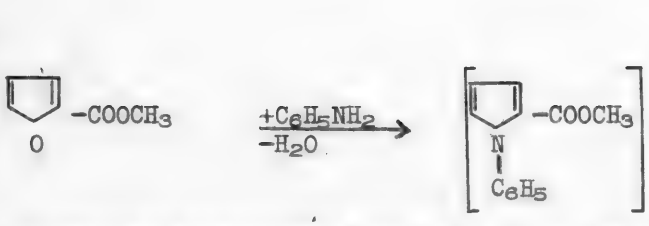
The N-phenylpyrrole might be formed in two possible ways at higher temperatures (350-475°):

1. The reaction involves the formation of the anilide of N-phenylpyrrole-α-carboxylic acid; hydrolysis of the latter yields N-phenylpyrrole-α-carboxylic acid, which is turned into N-phenylpyrrole by the evolution of carbon dioxide (Diagram I).

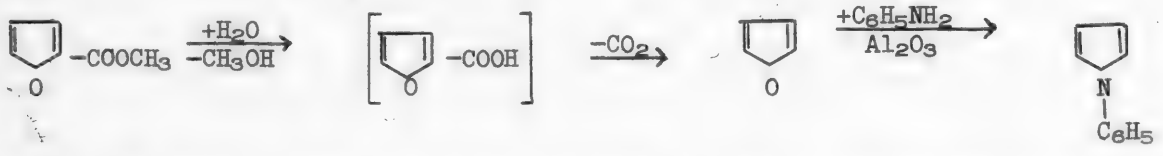
2. What is more likely, however, is a reaction in which the anilide of N-phenylpyrrole-α-carboxylic acid is not formed at all at 350-475°, the water evolved

during the replacement of the ring oxygen by the phenylimino group hydrolyzing the resulting methyl ester of N-phenylpyrrole-α-carboxylic acid; the free N-phenylpyrrole-α-carboxylic acid yields N-phenylpyrrole by giving off carbon dioxide (Diagram II).

I 

II 

Inasmuch as we secured furan as well as N-phenylpyrrole from the product of the reaction of methyl pyromucate with aniline at 350°, we might have supposed that the N-phenylpyrrole was synthesized from the furan itself at the instant the latter was formed from the pyromucic acid, which was in turn formed as the result of the hydrolysis of its ester, first by the water contained in the alumina and then by that evolved during dehydration:



But when furan is reacted with aniline at 400° the yield of N-phenylpyrrole is much lower than when the ester of pyromucic acid is reacted with aniline at the same temperature. As might have been expected, the presence of the carbomethoxy group in the α-position of the furan ring facilitates the replacement of the ring oxygen, which is why any other trend of the reaction, though possible, will exhibit a lower yield.

When methyl pyromucate is passed over alumina at 350°, it undergoes partial hydrolysis and decomposition: carbon dioxide, furan, and the unchanged ester were found in the products of catalysis. In this experiment, as in the preceding ones, the catalyst was covered with a carbonlike film. The methyl pyromucate undergoes almost no change at 350° when no alumina is present, the decomposition being negligible.

EXPERIMENTAL

1. Reaction of methyl pyromucate with aniline in the presence of Al_2O_3. Temperature 475°. A mixture of 8 g of methyl pyromucate:

B.p. 59-61° (3 mm); n_D^{20} 1.4873; d_4^{20} 1.1783; MR_D 30.07; Computed for $C_8H_8H_3=_2$. 30.20.

Literature data [2]: B.p. 181.3°; n_D^{20} 1.4871; d_4^{20} 1.1786.

and 24 g of freshly distilled aniline (1:4) was passed over alumina in a current of nitrogen at the rate of 5-6 drops per minute. The catalyzate (20 g) was extracted with ether and desiccated with fused potash. After the ether had been driven off, the residue was distilled in 3 mm vacuum; this yielded the following fractions: I – 57-60°, 14 g; II – 60-85°, 1 g; III – 85-90°, 1.5 g; the residue in the flask turned into tar.

Fraction I was aniline; n_D^{20} 1.5816; d_4^{20} 1.0186.

Fraction III was a substance with a m.p. of 58°, which fused at 60° after being twice recrystallized from aqueous alcohol, and fused at 61° after being sublimed. It exhibited an intense pyrrole reaction with pine shavings that had been wetted with concentrated hydrochloric acid, turning them purple. Found %: N 9.69. $C_{10}H_9N$. Computed %: N 9.78.

The analysis data, the melting point, and the properties all indicated that this substance was N-phenylpyrrole. The yield was 17% of the theoretical.

Literature data: M.p. 62° [3]; B.p. 234° [4]; M.p. 61-62° [5].

Temperature 400°. A mixture of 10 g of methyl pyromucate and 18.5 g of aniline (1:2) was used for the reaction. After suitable treatment of the catalyzate (18 g) and driving off the aniline, we secured a fraction with a b.p. of 85-87° at 3 mm and a m.p. of 61° (after sublimation), which was N-phenylpyrrole. The yield was 4 g, or 35% of the theoretical.

Temperature 350°. A mixture of 10 g of methyl pyromucate and 18 g of aniline (1:2) was used for the reaction. Suitable treatment of the resulting catalyzate (22 g) and distilling it from a Favorsky flask with a tall, narrow dephlegmator yielded 0.9 g of furan, with a b.p. of 31° (755 mm) and n_D^{20} 1.4212.

Literature data for furan: B.p. 31.2-31.6°; n_D^{20} 1.4236; d_4^{20} 0.9388 [6].

The residue was distilled in vacuum, and after the aniline had been driven off, we secured a fraction with a b.p. of 85-86° at 3 mm and a m.p. of 61° (after sublimation), which was N-phenylpyrrole. The yield was 2.5 g (22% of the theoretical).

Temperature 350°. 1 g of methyl pyromucate, 2.7 g of aniline (1:3), and 0.3 g of previously activated alumina were heated for 8 hours in a sealed tube. When the tube was opened, it was found to contain a considerable gas pressure. The reaction product was extracted with ether and desiccated with fused potash; the ether was driven off, and the residue was distilled in vacuum. Driving off the aniline (fraction with a b.p. of 53-80° at 2 mm; n_D^{20} 1.5810) yielded 0.2 g of crystals of N-phenylpyrrole, with a m.p. of 60°.

Temperature 310°. 1 g of methyl pyromucate, 2.7 g of aniline (1:3), and 0.3 g of activated alumina were heated for 8 hours in a sealed tube. The substance inside the tube crystallized partially. The crystalline substance and the catalyst were removed and washed with ether; the substance fused at 123° after recrystallization from alcohol.

Found %: N 7.53. $C_{11}H_9O_2$. Computed %: N 7.48.

The analysis data and the melting point indicated that the substance was pyromucanilide. The yield was 1.3 g (87.5% of the theoretical).

Data in the literature: m.p. 123.5° [7].

The liquid portion of the reaction product, combined with the wash ether, exhibited a slight pyrrole reaction with pine shavings wetted with concentrated hydro-

chloric acid. After desiccation and after the ether had been driven off, distilling the residue in vacuum yielded nothing but aniline (fraction with a b.p. of 57-85° at 3 mm; n_D^{20} 1.5821).

Temperature 270°. 2 g of methyl pyromucate, 5.5 g of aniline (1:3), and 0.5 g of activated alumina were heated for 9 hours in a sealed tube. The substance within the tube solidified; it exhibited a slight pyrrole reaction with pine shavings. The treatment described above yielded 2 g of pyromucanilide, with a m.p. of 122.5°. The yield was 68.5% of the theoretical.

Temperature 220°. Heating 2 g of methyl pyromucate with 5.5 g of aniline (1:3) for 8 hours in the presence of 0.5 g of activated alumina yielded 2 g of pyromucanilide, with a m.p. of 122.5°. The yield was 68.5% of the theoretical. The crude reaction product exhibited a weak pyrrole reaction with pine shavings.

Temperature 190°. 10 g of methyl pyromucate, 27 g of aniline (1:3), and 1 g of activated alumina were boiled for 15 hours over an oil bath in a flask fitted with a reflux condenser. The reaction mixture solidified. It was diluted with ether and filtered. After the ether had been driven off from the desiccated filtrate, the residue was distilled in a Wurtz flask, the following fractions being collected: I – b.p. 130-186°, 11.5 g; II – b.p. 186-196°, 0.5 g; III – b.p. 195-220°, a minute quantity of a substance that crystallized in the air-cooled condenser and exhibited an intense pyrrole reaction with pine shavings; squeezed out on a plate, the crystals fused at 58° and consisted of N-phenylpyrrole.

Aniline (b.p. 78-80° at 15 mm; n_D^{20} 1.5817) was recovered from Fraction II by distilling it in vacuum.*

Literature data: b.p. 184°; n_D^{20} 1.5863 [8].

After the crystalline reaction product had been recrystallized from alcohol, it fused at 123° and was found to be pyromucanilide. The yield was 8 g (54% of the theoretical). 3 g of the anilide was hydrolyzed by boiling it for 6 hours with 13.5 ml of 2N caustic soda in a flask fitted with a reflux condenser. The hydrolysis product yielded 1.2 g of aniline (b.p. 180-181° at 752 mm; n_D^{20} 1.5859) and 0.8 g of pyromucic acid, with a m.p. of 132-133°.

Temperature 190°. 5 g of methyl pyromucate and 13.5 g of aniline were boiled for 72 hours in a flask fitted with a reflux condenser. The reaction mass did not exhibit a pyrrole reaction with pine shavings, nor was any anilide formed.

2. Behavior of methyl pyromucate when in contact with Al_2O_3. 10 g of methyl pyromucate was passed over alumina at 350° in a current of nitrogen at the rate of 5-6 drops per minute. The carbon dioxide evolved was absorbed in a solution of barium hydroxide. First furan was driven off from the catalyzate (totaling 5.5 g), which had been desiccated with calcined potash; this was done in a Favorsky flask attached to a tall, narrow dephlegmator. At 31° 0.9 g of furan with n_D^{20} 1.4231 was driven off. Distillation of the residue yielded 4 g of the unchanged methyl pyromucate: b.p. 181° (759 mm).

3. Thermal stability of methyl pyromucate. 10 g of methyl pyromucate was passed through a tube filled with pieces of glass and heated to 350°, at the rate of 5-6 drops per minute in a current of nitrogen. The slight amount of carbon dioxide that was evolved was adsorbed in baryta water. The 9.2 g of catalyzate was desiccated with calcined potash and then distilled, only the unchanged methyl

* In this, as in all previous cases, the lowering of the refractive index is probably due to a trace of the unchanged ester, and, possibly, to a trace of methylaniline, which may be formed in the joint catalytic dehydration of aniline and methanol.

pyromucate (8.8 g) being recovered: b.p. 180-182°; n_D^{20} 1.4874.

4. Reaction of furan with aniline in the presence of Al_2O_3. In order to compare the ease with which the ring oxygen can be replaced in furan and in methyl pyromucate, we made a study of the reaction of furan with aniline in the presence of Al_2O_3 at 400° (the optimum temperature for the formation of N-phenylpyrrole from the ester of pyromucic acid).

A mixture of 10 g of furan and 27 g of aniline (1:3) was passed over alumina at 400° in a current of nitrogen at the rate of 5-6 drops per minute. The 32 g of catalyzate was extracted with ether and desiccated with calcined potash. After the ether had been driven off, the residue was distilled in vacuum; the following fractions were collected: I – b.p. 58-60° (4 mm); 20 g (aniline); II – b.p. 60-88° (4 mm), 3 g; and III – b.p. 88-89° (4 mm), 4.5 g; the residue in the flask turned into tar.

Fraction III was N-phenylpyrrole, which fused at 61° after sublimation (yield – 21% of the theoretical).*

SUMMARY

1. The reaction of methyl pyromucate with aniline in the presence of alumina at 350, 400, and 415° results in the formation of N-phenylpyrrole, with a yield of as much as 35% of the theoretical.

2. When methyl pyromucate is reacted with aniline in the presence of alumina at 190, 220, 270, and 310°, pyromucanilide is formed, only traces of N-phenylpyrrole being found.

3. At 350° methyl pyromucate undergoes partial hydrolysis and decomposition in the presence of alumina, giving rise to furan and carbon dioxide. When no alumina is present, the decomposition of the ester at 350° is negligible.

4. The conversion of methyl pyromucate into N-phenylpyrrole takes place under milder conditions and with a higher yield (400°; 35% yield) than the conversion of furan itself (400°; 21% yield). Hence, the carbomethoxy group, which is in the α-position in the furan ring, greatly aids the replacement of the ring oxygen in this compound by some other atom.

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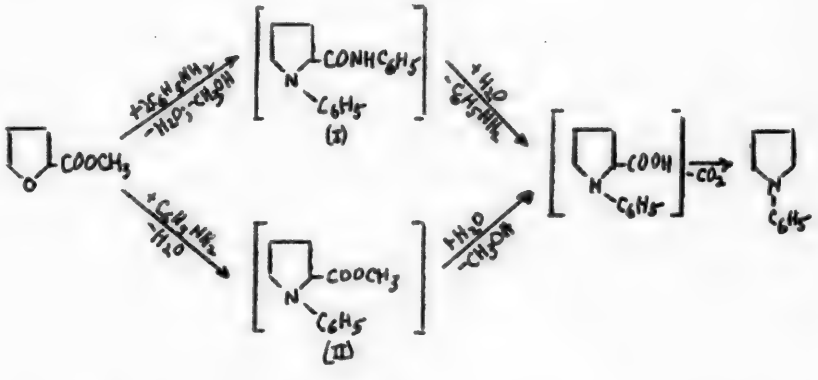
*The yield of N phenylpyrrole was 24% of the theoretical at 465° [5].

XXXI. THE REACTION OF METHYL TETRAHYDROPYROMUCATE WITH ANILINE

Yu. K. Yuriev and E. G. Vendelshtein

In our previous report we showed that the reaction of methyl pyromucate with aniline at 400° in the presence of alumina results in the formation of N-phenylpyrrole, instead of the methyl ester of N-phenylpyrrole-α-carboxylic acid [1]. In the present research aniline has been reacted with methyl tetrahydropyromucic acid. The reaction mixture was passed over alumina at 360° instead of 400°, inasmuch as the conversion of furanidine compounds into heterocyclic compounds containing nitrogen takes place at milder temperature conditions. It was found that the reaction of methyl tetrahydropyromucate with aniline results in the formation of N-phenylpyrrolidine instead of the methyl ester of N-phenylpyrrolidine-α-carboxylic acid. The formation of N-phenylpyrrolidine was accompanied by the copious evolution of carbon dioxide. The formation of N-phenylpyrrolidine from methyl tetrahydropyromucate may be thought of as occurring in one of the two reactions outlined below:



Each of these reactions involves the intermediate formation of N-phenylpyrrolidine-α-carboxylic acid, which gives up carbon dioxide to yield N-phenylpyrrolidine. As a rule, pyrrolidine compounds are produced with higher yields from the corresponding heterocyclic compounds containing oxygen than from pyrrole compounds [2]. In this case, however, the yield of N-phenylpyrrolidine (13%) was lower than the yield of N-phenylpyrrole (35%) in the analogous conversion of methyl pyromucate. The lower yield of N-phenylpyrrolidine is probably due to the low stability of the methyl tetrahydropyromucate itself and of the N-phenylpyrrolidine-α-carboxylic acid; the

latter fuses at 215-220° with decomposition, as we know [3].

When methyl tetrahydropyromucate was passed over alumina at 360°, it was decomposed, carbon dioxide, propylene, and methanol being formed. Hence, the ester was first hydrolyzed, forming tetrahydropyromucic acid, which turned into furanidine by giving off carbon dioxide; above alumina at 360° the furanidine was decomposed as had been the case at 400° [4], i.e., with the evolution of propylene. Heating tetrahydropyromucic acid to 300-305° caused vigorous decarbonization, with the formation of furanidine (tetrahydrofuran).

EXPERIMENTAL

1. Methyl Tetrahydropyromucate

This was prepared by catalytically hydrogenating methyl pyromucate. 33 g of methyl pyromucate (b.p. 59-61° at 3 mm; n_D^{20} 1.4873; d_4^{20} 1.1793; MR_D 30.77; computed 29.95) was passed at a rate of 2-3 drops per minute in a current of hydrogen through a tube filled with palladinized asbestos and heated to 160°. After all the ester had been used up, 5 g of furan was passed through the tube to remove the product completely from the catalyst.* After the furanidine (b.p. 64-66°; n_D^{20} 1.4083 had been driven off, the methyl tetrahydropyromucate was distilled into a small dephlegmator: b.p. 179.5 180.5° at 736 mm; n_D^{20} 1.4371; d_4^{20} 1.1080; MR_D 30.76, computed 30.88. The yield was 26.5 g (78% of the theoretical). Methyl tetrahydropyromucate is not described in the literature.

2. Reaction of Methyl tetrahydropyromucate with Aniline in the Presence of Alumina

A mixture of 10 g of methyl tetrahydropyromucate and 27 g of freshly distilled aniline (1:3) was passed at the rate of 5-6 drops per minute in a current of nitrogen through a tube filled with alumina at 360°. A copious precipitate of barium carbonate settled out in a bottle filled with baryta water, connected to the receiver. The catalysis product was extracted with ether. After the ether had been driven off from the ether extract, which had been desiccated with anhydrous sodium sulfate, the residue was distilled in 6 mm vacuum, the following fractions being collected:

I. 59-63° (14 g) – unchanged aniline; II – 63-68° (3 g); III – 68-112° (1.7 g); IV – 112-114° (1.2 g). After Fractions III and IV had been redistilled in vacuum, 1.5 g of a substance having the following constants was recovered: b.p. 104-105° at 4 mm; n_D^{20} 1.5840; d_4^{20} 1.0164. The boiling point, the refractive index, and the specific gravity of the substance recovered are those of N-phenylpyrrolidine. The picrate produced from the mixed ether solutions of the substance recovered and picric acid fused at 116° (after recrystallization from alcohol), which is the melting point of N-phenylpyrrolidine picrate. A test sample, mixed with N-phenylpyrrolidine picrate exhibited no depression of the melting point: m.p. 116°.

> Literature data for N-phenylpyrrolidine. Braun and Lemke [5] – b.p. 124° at 14 mm; picrate m.p. 114°; Signaigo and Adkins [6] – b.p. 110-116° at 9 mm; n_D^{25} 1.5803; d_4^{25} 1.026; picrate m.p. 115-116°; Yu.K.Yuryev [7] – b.p. 114° at 9 mm; n_D^{20} 1.5853; d_4^{20} 1.0183; EM_D 1.86; picrate m.p. 116°.

Hence, the reaction of methyl tetrahydropyromucate with aniline at 350° in the presence of alumina results in the formation of N-phenylpyrrolidine. The yield was 1.5 g (13% of the theoretical).

3. Behavior of Methyl Tetrahydropyromucate at 360° With Alumina

5 g of methyl tetrahydropyromucate was passed at the rate of 5-6 drops per minute in a current of nitrogen over alumina at 360°. As the ester passed over the catalyst, intense evolution of carbon dioxide was observed; this was seen in the settling out of a copious precipitate of barium carbonate in the wash bottle

*The catalysis product was desiccated with calcium chloride and distilled.

filled with baryta water and attached to the receiver. The catalysis product, only an insignificant quantity of which was recovered, contained water and methanol (positive reaction for the formation of iodoform). After the gaseous reaction products had been passed through the baryta water, they entered a wash bottle containing bromine. After the excess bromine had been removed from the latter with an alkali solution, the bottle's contents yielded 1.6 g of a dibromide possessing the following constants:

B.p. 139.5-141° at 755 mm; n_D^{20} 1.5181; d_4^{20} 1.9304; MR_D 31.70. computed 31.08.
0.2525 g substance: 0.4682 g AgBr. Found %: Br 78.92. $C_3H_6Br_2$. Computed %: Br 79.15.

Its constants and the analysis data indicated that the resultant dibromide was 1,2-dibromopropane.

4. Behavior of Tetrahydropyromucic Acid When Heated

a) Preparation of tetrahydropyromucic acid. 10 g of methyl tetrahydropyromucate and 41 ml of 2 N sodium hydroxide were boiled for four hours in a flask with a reflux condenser. After the reaction mixture had cooled, it was acidulated with 30% sulfuric acid (until its reaction was acid with Congo), and the tetrahydropyromucic acid was extracted with ether (in an extractor) for 32 hours. The ether extract was desiccated with anhydrous sodium sulfate, and the ether was driven off, first at atmospheric pressure and then in vacuum (at 50°). When it cooled, the tetrahydropyromucic acid was a pasty, finely crystalline mass. The yield was 6.6 g (76% of the theoretical).

4.365 mg substance; 8.199 mg CO_2; 2.790 mg H_2O.
Found %: C 51.23; H 7.15. $C_5H_8O_3$. Computed %: C 51.72; H 6.89.
Literature data for Tetrahydropyromucic Acid: Weinhaus and Sorge [8]: m.p. 21°; b.p. 131° at 14 mm; 145° at 25 mm.

b) Decarbonization of tetrahydropyromucic acid. 6 g of tetrahydropyromucic acid was heated in a flask fitted with a thermometer extending to the bottom of the flask and a dephlegmator connected to a coil condenser. The condenser was connected to a receiver chilled with a snow-salt mixture, the latter in turn being connected to a wash bottle containing baryta water. Slight evolution of carbon dioxide set in at 270-280°. At 300-305°, the evolution of carbon dioxide was vigorous; at this temperature furanidine (tetrahydrofuran) began to distil over and was collected in the receiver. Distillation over sodium yielded 1.5 g of furanidine: b.p. 65° at 755 mm; n_D^{20} 1.4088; d_4^{20} 0.8899.

Literature data for furanidine: N.Ya.Demyanov, [9] – b.p. 64-65° at 760 mm; n_D^{21} 1.4076; d_4^{21} 0.888. N.I.Shuikin and E.M.Chilikina [10] – b.p. 65-65.2° at 746 mm; n_D^{20} 1.4090; d_4^{20} 0.8897; Yu.K.Yuryev [11] – b.p. 65-65.5° at 760 mm; n_D^{20} 1.4091; d_4^{20} 0.8899.

SUMMARY

1. The reaction of methyl tetrahydropyromucate with aniline and alumina at 360° results in the formation of N-phenylpyrrolidine instead of the methyl ester of N-phenylpyrrolidine-α-carboxylic acid.

2. Methyl tetrahydropyromucate decomposes at 360° in the presence of alumina; carbon dioxide, propylene, and methanol were found in the decomposition products.

3. When tetrahydropyromucic acid is heated to 300-305°, it gives off carbon dioxide and yields furanidine.

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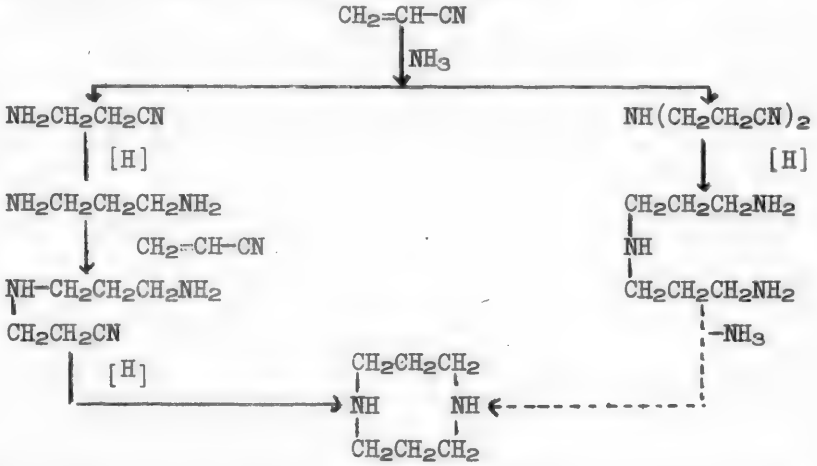
*See CB translation, this issue

SYNTHESES EMPLOYING ACRYLONITRILE

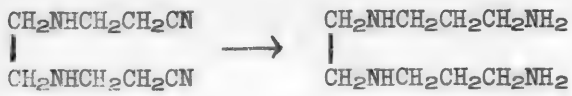
XII. THE SYNTHESIS OF SOME ANALOGS OF SPERMINE AND SPERMIDINE

A. P. Terentyev, A. N. Kost, and K. I. Chursina

Spermine ($NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NHCH_2CH_2CH_2NH_2$) and spermidine ($NH_2CH_2CH_2CH_2NHCH_2CH_2CH_2CH_2NH_2$), found in male semen as phosphates, are widely employed in medicine and are usually obtained from the pancreatic gland of cattle. The structure of spermine and spermidine has been demonstrated accurately enough in the research of Dudly and Wrede [1]. In 1948, Schultz [2] published a method of synthesizing spermine by dicyanethylating putrescine, with subsequent reduction. In the present paper we describe the preparation of several analogs of spermine and spermidine, whose synthesis can be effected with acrylonitrile. In our preceding report [3], we described the preparation of one of the homologs of spermine, namely, di-(γ-aminopropyl)-amine, by reducing β,β'-iminodipropiodinitrile. In our present research we effected the monocyanethylation of trimethylenediamine and reduced the resulting aminonitrile with sodium in butyl alcohol. This replaced the linear di-(γ-aminopropyl)-amine with a cyclic analog, i.e., 1,5-diazacyclo-octane, with good yield. We were able to isolate this compound in small quantities from the product of the reduction of β,β'-iminodipropiodinitrile.



The dicyanethylation product of ethylenediamine [4] was similarly reduced with sodium in butyl alcohol, a homolog of spermine, namely, N,N'-di(γ-aminopropyl)-ethylenediamine, being produced:



EXPERIMENTAL

Cyanethylation of trimethylenediamine. A) Mol per mol. 10.6 g (0.2 mol) of acrylonitrile was cautiously added, with stirring and external cooling, to 14.8 g (0.2 mol) of anhydrous trimethylenediamine, prepared by reducing β-aminopropionitrile [3]. The reaction is accompanied by the evolution of heat, but the mixture should not be chilled below 10°, as otherwise the reaction comes to a stop. To complete the reaction the mixture was gradually heated to 40-45°, and after the vigorous reaction was finished, heating was continued for another two hours over a water bath (with a reflux condenser). Then the mixture was quickly distilled in vacuum in a current of anhydrous nitrogen. This yielded 20.3 g of monocyanethylation product, or 80% of the theoretical. B.p. 200-210° at 3 mm. We also secured about 3 g of a high-boiling fraction, with a b.p. of 230-270° at 3 mm with partial decomposition. This fraction consisted principally of a dicyanethylation product.

B) 1 Mol per 2 Mols. The reaction was performed as in the preceding experiment, but with 4.5 g (0.06 mol) of trimethylenediamine and 7.0 g (0.13 mol) of acrylonitrile. The first vacuum distillation yielded 5.3 g of monocyanethylation product (70% of the theoretical) and 2.5 g of dicyanethylation product (23% of the theoretical). Both of these products were purified by means of triple vacuum distillation in a current of anhydrous nitrogen. The monocyanethylation product, i.e., N-(β-cyanethyl)-trimethylenediamine, is a thick, colorless oil, highly hygroscopic and attracting carbon dioxide from the air. B.p. 203-206° at 3 mm; 214-218° at 6 mm; n_D^{20} 1.4762; d_4^{20} 0.9725; MR_D 36.90; computed 36.82.

Hydrochloride – colorless needles from water, that darken at temperatures above 180°.

5.690 mg substance: 1.046 ml N_2 (18°, 745 mm). 4.052 mg substance: 0.748 ml N_2 (19°, 745 mm). Found %: N 21.14, 21.16. $C_6H_{13}N_3 \cdot 2HCl$. Computed %: N 21.00.

The dicyanethylation product, i.e., N,N'-di-(β-cyanethyl)-trimethylenediamine, is an extremely viscous, colorless liquid. B.p. 263-265° at 3 mm; 271.5° at 6 mm.

n_D^{20} 1.4826; d_4^{20} 1.0168; MR_D 50.58; computed 50.72.

4.446 mg substance; 1.227 ml N_2 (22°, 739 mm). 4.597 mg substance: 1.268 ml N_2 (22°, 739 mm). Found %: N 31.06, 30.98. $C_8H_{16}N_4$. Computed %: N 31.09.

Preparation of 1,5-diazacyclo-octane. We prepared 1,5-diazacyclo-octane as its hydrochloride by reducing N-(β-cyanethyl)-trimethylenediamine with sodium in alcohol as follows: 12.7 g (0.1 mol) of the aminonitrile was dissolved in 250 ml of n-butyl alcohol, heated to 100°, and poured all at once over 15 g of metallic sodium, which had been placed in a round-bottomed flask fitted with a reflux condenser.* The mixture was then heated over a water bath until all the sodium had dissolved, the alcohol was driven off, and the resulting amine was distilled with steam superheated to 125-135° in a solution of hydrochloric acid. Distillation was continued for about 12 hours (distillate volume = 3.0 to 3.5 liters), after which the alcohol layer was removed, washed four times with small batches of water, and all the aqueous solution evaporated to dryness. This yielded 9.7 g, i.e., 82% of the theoretical, of 1,5-diazacyclo-octane dihydrochloride. It consisted of colorless prisms with a m.p. of 270° after double recrystallization from a water-methanol mixture.

*Copper

3.820 mg substance: 0.48020 ml N_2 (30°, 746 mm); 2.900 mg substance: 0.35476 ml N_2 (28°, 746 mm). Found %: N 13.90, 13.62. $C_8H_{14}N_2 \cdot 2HCl \cdot H_2O$. Computed %: N 13.79.*

Picrate – needles from water. M.p. 226° (decomp.).

5.495 mg substance: 0.91630 ml N_2 (27°, 761 mm). 4.210 mg substance: 0.68306 ml N_2 (28°, 761 mm). Found %: N 19.01, 18.61. $C_8H_{14}N_2 \cdot 2C_8H_3O_7N_3 \cdot H_2O$. Computed %: N 18.96.**

Reducing N,N'-di-(β-cyanethyl)-ethylenediamine. 16.6 g (0.1 mol) of N,N'-di-(β-cyanethyl)-ethylenediamine was reduced in the usual manner with 30 g of metallic sodium in 450 ml of n-butyl alcohol. The butyl alcohol and the polyamine were driven off from the reaction mixture in the course of 12 hours with steam superheated to 135-140° (with dilute sulfuric acid in the receiver). The alcoholic layer was removed and washed with water, and the water layer together with the wash waters were evaporated to dryness over a water bath. This yielded 12.6 g of the crude hydrochloride, i.e., 72% of the theoretical. It was purified by being twice recrystallized from water. Colorless needles, which turn dark above 150°.

4.017 mg substance: 0.58506 ml N_2 (25°, 755 mm). 3.225 mg substance: 0.48020 ml N_2 (26°, 755 mm). Found %: N 16.56, 16.91. $C_8H_{22}N_4 \cdot 4HCl \cdot H_2O$. Computed %: N 16.57.

SUMMARY

1. Trimethylenediamine has been cyanethylated. Reduction of the monocyanethyltrimethylenediamine with sodium and butyl alcohol yielded 1,5-diazacyclo-octane, which is an analog of piperazine.

2. Reduction of the dicyanethylation product of ethylenediamine yielded N,N'-di-(γ-cyanethyl)-ethylenediamine, a homolog of spermine.

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*%N = 17.46 for a compound of linear structure

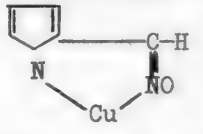
**%N = 20.55 for a compound of linear structure

STEREOISOMERISM OF THE OXIMES OF 2 PYRROLEALDEHYDE AND 2-PYRROLE KETONES [1]

A. P. Terentyev and A. N. Makarova

The stereochemistry of compounds of trivalent nitrogen was first discovered and most fully explored in the oximes of aldehydes and ketones. It should be noted that far from all oximes have been discovered to have second isomers. Most of the aliphatic aldehydes and ketones form only one isomer. Up to the present time the reason for this is unknown. Instances of the extreme lability of one of two known forms are not uncommon. Aromatic aldehydes are usually known in fairly stable stereoisomers. Fairly stable stereoisomers of the oximes have also been secured in the simplest heterocyclic compounds, furfural and α-thiophenaldehyde. But up to the present time not a single instance of the existence of stereoisomeric forms has been described for the numerous known oximes of aldehydes and ketones of pyrrole. We performed this research in a desire to fill this hiatus. In several instances, we succeeded in providing a positive answer to the question of the existence of stereoisomeric oximes of the α-aldehyde and α-ketones of pyrrole and in determining their configurations.

2-Pyrrolaldoxime. The only presently known oxime of α-pyrrolaldehyde (m.p. 164°) was synthesized in 1900 by Bamberger and Djierdjian [2], who did not deal with the problem of its configuration, however. In 1927, Emmert and Diehl [3] made a study of the peculiarities and the structure of α-pyrrolaldehyde and happened to investigate the formation of a copper salt of a pyrrolaldoxime. It was secured as an amorphous brown powder by boiling an alcoholic solution of the oxime with an ammoniacal solution of copper. An approximate analysis (not cited in the paper) indicated that it contained 1 atom of copper per molecule of the oxime. Without going into the problem of configuration, the authors picture the structure of this salt as follows:



i.e., as if they adopted a syn configuration for it. In 1933, H.Fischer and H.Orth [4] demonstrated that when pyrrolaldoxime is heated with acetic anhydride and sodium acetate, 2-acetyl-5-cyanpyrrole is produced. The authors did not deal with the question of the configuration of the oxime they had investigated. Furthermore, it may be concluded with all due caution, from their observations, that the pyrrolaldoxime with a m.p. of 164° probably has an anti configuration.

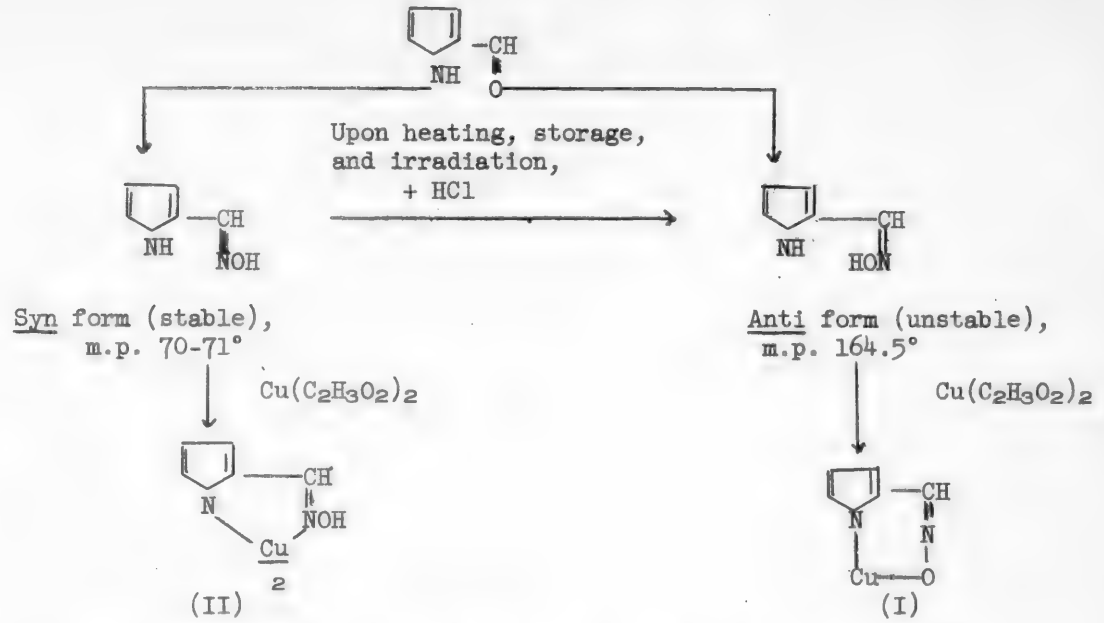
We made a careful study of the reaction involved in the preparation of α-pyrrolaldoxime. We prepared α-pyrrolaldehyde by the Chelintsev and Terentyev method [5], reacting pyrrolemagnesium bromide with ethyl formate. Heating the aldehyde solution with hydroxylamine hydrochloride and an excess of soda caused the oxime to settle out as minute crystals. The melting point was that given in the literature (164°),

after crystallization from chloroform. On the assumption that the second stereoisomer might not be very stable, we repeated the oximation, using no heat. The oxime began to settle out of solution after 0.3 g of pyrrolaldehyde had been allowed to stand for 12 hours. Two kinds of crystals were produced. Most of them (0.2 g) were minute crystals resembling those obtained in the first experiment, with a m.p. of 164°. Large crystals, more readily soluble and resembling flakes of mica, also precipitated out slowly. They were removed by means of tweezers, and totaled about 0.1 g. Their melting point was 70-71°. They lost their luster when dried and kept in storage. These large crystals proved to be the sought-for unstable second isomer, which readily isomerizes to the stable isomer with a m.p. of 164°. In fact, when this compound was heated in a capillary, it fused at 70-71°; the transparent melt began to grow cloudy at 120-130°; the mass solidified at about 150-160°, melting anew at 164°. The product of thermal isomerization exhibited no depression when mixed in a test sample with crystals of the first experiment. A mixture of the first and second forms, which fused within wide limits, 145-160°, crystallized completely and fused again at 163-164°. The low-melting isomer is really quite unstable. It is converted into the high-melting isomer even when recrystallized from boiling water or alcohol, when exposed to hydrochloric acid, or when its benzene solution is irradiated with a quartz lamp. The flakes of the low-melting form gradually deliquesce when kept on a sheet of filter paper, turning into minute crystals with a m.p. of 164° within 10 to 15 days. But when carefully purified by crystallization from ether, this form may be stored for a fairly long time without noticeable change. Hydrolysis with hydrochloric acid yielded the original pyrrolaldehyde.

As was established by L.A.Chugaev as long ago as 1906 [6] and subsequently confirmed in a number of instances by P.Pfeiffer [7], the configuration of the oximes can be determined in such cases with complete reliability from the composition and properties of their Cu and Ni salts. Only oximes of a given configuration can form inner salts of chelate structure. Blatt [8] also employed this method. α-Pyrrolaldoxime, which possesses imino hydrogen that can be readily replaced by a metal, happens to be a case to which the Chugaev method of determining configuration is fully applicable. Possessing the two stereoisomeric oximes, we compared their behavior with copper acetate. A dilute solution of the high-melting isomer did not yield a precipitate with this salt, the blue color of the solution merely changing to green. When strong solutions were used, a voluminous green precipitate of the copper salt was precipitated; this salt was readily soluble in dilute mineral acids, acetic acid, and ammonia. Analysis showed that the salt contained 1 atom of copper per molecule of the oxime. A salt of this composition and nature is not a complex inner salt and must be of the anti form (I). The low-melting form of pyrrolaldoxime immediately yielded a brown precipitate with copper acetate, even in highly dilute solutions; this precipitate was insoluble in dilute acids or ammonia. The salt dissolved in pyridine, coloring the solution brown. Analysis showed that this salt contained 1 atom of copper to approximately 2 molecules of the oxime. Hence, the composition and the nature of this salt show that it is a typical complex inner salt, which indicates a syn configuration (II) for pyrrolaldoxime.

Hence, all the conversions of the 2-pyrrolaldoximes may be represented as follows: (cf p. 297).

In conclusion, it may be of some interest to cite some comparisons that tend to bear out our conclusions as to the configuration of the pyrrolaldoximes. There is a rule, which applies to the aldoximes almost without exception, to the effect that the syn forms are more easily fusible than the anti forms. We cite several typical examples of this (cf Table). It is also worthy of note that benzaldehyde and most other aromatic aldehydes yield syn isomers upon oximation, these being more stable.



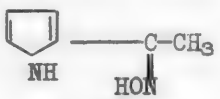
In the aliphatic aldehydes, it is the anti forms that are more stable. The heterocyclic aldoximes (thiophenaldehyde or furfural) exhibit nearly identical stability for both forms [9]. Thus, the oximes of α-pyrrolaldehyde fall into the same class as the others as far as their stability is concerned, resembling the aliphatic aldoximes.

Melting Points of Aldoximes

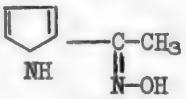
	Syn form	Anti form
Benzaldehyde	35°	132°
Furfural	75-76	91-92
2-Thiophenaldehyde..	oil	133
2-Pyrrolaldehyde....	70-71	164
Enanthic aldehyde...	oil	57-58

Oximes of 2-acetylpyrrole. We prepared the oxime of 2-acetylpyrrole by the method described by Ciamician and Dennstedt [10], i.e., by boiling the ketone in methanol for 1.5 hours with hydroxylamine and soda. The oxime fused at 145°, the figure given in the literature, after crystallization from water. When we repeated the preparation of the oxime, we noticed that boiling the reaction mixture for a long time caused the reaction product to have a "diffuse" melting point. After boiling the mixture for 10 hours, we secured a product with a m.p. of 85-90°. Two substances were secured by recrystallization from water and alcohol. One, acicular in form, had a m.p. of 145°, and its fusion test sample indicated that it was identical with the known isomer of the oxime. The other was a finely crystalline powder, with a m.p. of 82°; it was readily soluble in water, alcohol, ether, and benzene. Analysis indicated that it was an isomer of the former. Hydrolysis with hydrochloric acid yielded the original acetylpyrrole. We used the Chugaev method, which we had employed for the pyrrolaldoximes, to establish the configuration: the formation of complex inner compounds with copper salts. The already-known high-melting oxime (m.p. 145°) was dissolved in ether and agitated with a saturated solution of copper acetate. The only change noticed was a change in the color of the solution, from blue to green. After the solution had been allowed to stand for two hours, a salt precipitate settled out, which was soluble in acids and ammonia. Analysis showed that it had 1 atom of copper per molecule of the oxime. Thus, this salt is ionic, rather than an inner complex, in composition and character. Evidently, the

high-melting oxime has the structure of anti-methylpyrryl ketoxime (I). The newly produced low-melting oxime (m.p. 82°) immediately yielded a copious brown precipitate when it was agitated in ether solution with saturated aqueous solution of copper acetate. The composition and nature of this salt indicate that it is an inner coordination compound. It has one atom of copper to 2 molecules of the oxime. It is insoluble in dilute acids or ammonia. Its solution in pyridine is brown. It is obvious that these properties class the original oxime as syn-methylpyrryl ketoxime (II).



(I)
M.p. 145°



(II)
M.p. 82°

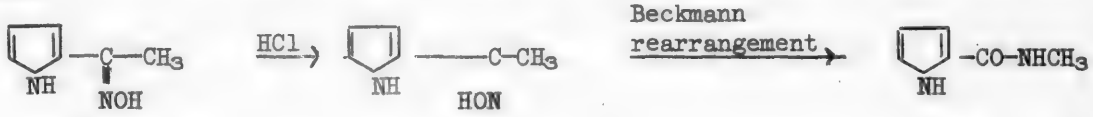
The properties and the reciprocal conversions of the two oxime forms indicate that their stabilities are nearly identical.

Anti-methylpyrryl ketoxime, m.p. 145°	Syn-methylpyrryl ketoxime, m.p. 82°
Forms a crystalline salt with a solution of HCl in acetone	No salt is formed
Evolves $2CH_4$ when reacted with CH_3ZnI; decomposition with water yields the original oxime with a m.p. of 145°	Evolves $2CH_4$ when reacted with CH_3ZnI; decomposition with water yields a mixture of oximes.
Heating to 160° converts it into the low-melting isomer	
	Converted to the High-melting form when HCl is passed through an ethereal solution.
	Irradiating a benzene solution with a quartz lamp causes partial conversion to the high-melting isomer.

In some instances a Beckmann rearrangement may also serve as a method of determining the configuration of oximes. As we know, in this rearrangement the hydroxyl group changes position with the radical in an anti position to it. It is risky to rely upon this method completely, however, inasmuch as the acid agents employed for the rearrangement may cause isomerization of the original oxime itself. We were interested in effecting a Beckmann rearrangement of the oximes of acetylpyrrole because this reaction had not been applied to the pyrrole series as yet. Moreover, if isomerization did not occur, we might expect the anti-methylpyrryl ketoxime to yield methyl pyrrolecarboxamide-2, while the syn-methylpyrryl ketoxime would yield the acetyl derivative of 2-aminopyrrole. However, the production of the latter, though highly desirable, is hardly likely, owing to the ease with which the low-melting form of the oxime is isomerized to the high-melting isomer when acted upon by acid agents, as well as to the extraordinary instability of pyrrole amines.

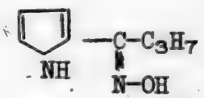
After a series of tests, we obtained the best results for the anti-methylpyrryl ketoxime (m.p. 145°) by performing the reaction in absolute ether, reacting the oxime with powdered phosphorus pentachloride, the mixture being chilled with snow and salt. The reaction product was added to a soda solution, similarly chilled.

The ether extract desiccated with calcium chloride. The residue left after the ether had been evaporated was recrystallized from water. White crystals with a m.p. of 151-152°. They sublime without noticeable decomposition. An experiment performed under the same conditions with the low-melting oxime (m.p. 82°) yielded the same substance with a m.p. of 151-152°. Considerable tarring took place. We identified the reaction product by synthesizing the expected methyl pyrrolecarboxamide-2 (from pyrrolecarbonyl chloride and methylamine). Its m.p. was 151° and a fusion mixed test sample indicated that it was identical with the product of the Beckmann rearrangement of the two oximes. It is thus evident that the action of phosphorus pentachloride or hydrogen chloride isomerizes syn-nethylpyrryl ketoxime into the anti isomer.



m.p. 82° m.p. 145° m.p. 151°

Oxime of 2-butyrylpyrrole. B.Oddo synthesized 2-butyrylpyrrole in 1910 [11] from pyrrolemagnesium iodide and butyryl chloride. In 1914 Chelintsev and Terentyev [12] proposed to prepare pyrrole ketones by reacting esters with organo-magnesium derivatives of pyrrole; they also synthesized 2-butyrylpyrrole in this way. The oxime of this ketone was not described in the literature. As our tests showed, it is very difficult to prepare the oxime of butyrylpyrrole. Only after boiling the ketone with an aqueous solution of hydroxylamine hydrochloride and an excess of soda for 8 hours were we able to synthesize the oxime. It fused at 119° after having been recrystallized from water as lustrous flakes. It is readily soluble in ether, alcohol, benzene, and chloroform. It does not form crystals of the hydrochloride when reacted with hydrogen chloride dissolved in acetone. The oxime proved to be highly stable; it was oxidized to the original ketone with difficulty. Numerous attempts to synthesize a second stereoisomer were without success. To determine the configuration of this single form of the oxime we resorted to the method of forming a copper salt. The test was made as previously with the oximes of 2-acetylpyrrole. The copper salt was produced as easily as the inner complex salt of syn-methylpyrryl ketoxime. This indicates that the oxime of 2-butyrylpyrrole we had synthesized has the configuration of syn-propylpyrryl ketoxime (III).

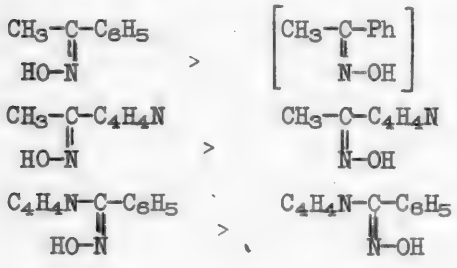


m.p. 119°
(III)

Oximes of 2-benzoylpyrrole. There is some disagreement in the literature regarding the oxime of 2-benzoylpyrrole. In 1904, A.Pictet [13] described this compound, prepared in the usual manner, as tiny needles (from water) with a m.p. of 147°. In 1912, B.Oddo and Dainotti [14] made an unsuccessful endeavor to synthesize this compound by varying the reaction conditions. At the start we were also unable to synthesize this oxime. The reaction was very difficult, involving hours (50 to 60 hours) of boiling an aqueous solution of benzoylpyrrole with hydroxylamine hydrochloride and soda. The appearance and the melting point of the oxime corresponded to those of the product synthesized by Pictet. This isomer, with a m.p. of 147°, was anti-phenylpyrryl ketoxime, to judge by the properties of its copper salt. In fact, when an ether solution of the oxime was mixed with an aqueous solution of copper acetate, no complex inner salt was formed. Only after prolonged agitation was an ionic salt produced; analysis showed that it contained 1 atom of copper per molecule of oxime. We prepared the other form of the oxime of 2-benzoylpyrrole as follows. 0.2 g of benzoylpyrrole was boiled for 30 hours with a solution of 0.2 g of hydroxylamine hydrochloride and 1.1 g of soda. The reaction

product had a very "diffuse" melting point (60-120°). It was carefully recrystallized from a water-alcohol mixture. Two substances were recovered: one was identified by its m.p. of 147° and by the melting point of a mixed test sample with the oxime form described above; the other crystallized from water as powdery crystals with a m.p. of 58°. It was readily soluble in organic solvents, and proved to be the sought-for second form of the oxime. The proofs thereof were as follows: analysis of the compound; the formation of the initial benzoylpyrrole after hydrolysis; and the fact that the low-melting isomer was converted into the high-melting one by heating to 150-160°. Passing hydrogen chloride through an ethereal solution of the low-melting form and then treating with soda produced the oxime with a m.p. of 147°. Evidently, this low-melting oxime is much less stable than the high-melting one. We were unable to recover even a minute quantity of the low-melting oxime even after many hours of irradiating a benzene solution of the oxime with a m.p. of 147° with a quartz lamp. As was to have been expected, testing an ether solution of the oxime with a m.p. of 58° with copper acetate yielded a brown salt that was an inner coordination compound. Unfortunately, we did not have enough of the substance available to perform an analysis.

Comparison of the properties of the ketoximes. We were interested in a comparison of the stability of several analogous ketoximes. As a rule, the more stable isomers of the oxime are those in which the hydroxyl group is on the same side of the molecule as the aliphatic radical. We know, for example, that acetophenoxime is stable only in one form, in which the hydroxyl is on the same side as the alkyl radical. α-Acetylthiophenoxime likewise exists in only one analogous form. The chemical nature of the pyrrole in this compound is close to that of an alkyl. And, as we have seen, the oxime of 2-acetylpyrrole may exist in two forms, but the more stable one is the form in which the hydroxyl group is in the syn position to the methyl group. This is even more marked in the case of the propyl radical in the oxime of 2-butyrylpyrrole. In this oxime both of the stereo forms have about the same stability [15], which might be expected in view of the strongly "aromatic" nature of thiophene. Pyrrole, as the more "aliphatic" group, yields 2 forms of oximes of 2-benzoylpyrrole, but the much more stable form is the one where the hydroxyl group is alongside the pyrrole.



EXPERIMENTAL

Synthesis of methyl pyrrolecarboxamide-2. The pyrrolecarboxylic acid-2 was prepared by B.Oddo's method [17], passing carbon dioxide through an ether solution of pyrrole-magnesium iodide. M.p. 204°. We then prepared its acid chloride by treating it with thionyl chloride. A solution of 2.3 g of thionyl chloride in 10 ml of chloroform was added drop by drop, with deep chilling, to a solution of 1.4 g of pyrrolecarboxylic acid in 10 ml of chloroform. After the reaction was complete, the chloroform was evaporated at reduced pressure. The acid chloride was extracted with ether. Needles with a m.p. of 90°. The yield was approximately 1 g (60% of the theoretical). A current of methylamine, prepared by reacting methylamine hydrochloride with solid caustic soda, was passed through a chilled solution of 1 g of the acid chloride in ether. The resulting precipitate was washed with water, desiccated, and recrystallized from benzene. M.p. 151°. Yield: 0.85 g (60% of the theoretical).

Oximes of 2-Pyrrolaldehyde

Analyses	Anti-form, m.p. 164°	Syn form, m.p. 70-71°
Determination of the number of active H atoms [16]	0.0357 g substance: 15.80 ml CH_4 (19°, 738 mm). Found: 1.95 active H atoms	0.0374 g substance: 16.80 ml CH_4 (18.8°, 738 mm). Found: 1.98 active H atoms
Analysis of the Cu salt	4.285 mg substance: 2.475 mg CuO. 3.700 mg substance: 2.140 mg CuO. Found %: Cu 36.73, 36.77. $C_5H_5ON_2Cu$. Computed %: Cu 37.00	3.505 mg substance: 1.100 mg CuO. 3.345 mg substance: 1.055 mg CuO. Found %: Cu 25.30, 25.20. $(C_5H_5ON_2)_2Cu$. Computed %: Cu 22.56.

Oximes of 2-Acetylpyrrole

Analyses	Anti form, m.p. 145°	Syn form, m.p. 82°
Determination of the number of active H atoms [16]	0.0447 g substance: 16.40 ml CH_4 (19°, 738 mm). Found: 2.03 active H atoms	0.0357 g substance: 14.75 ml CH_4 (16.2°, 735 mm). Found: 1.99 active H atoms
Analysis of the Cu salt	3.530 mg substance: 1.502 mg CuO 3.600 mg substance: 1.545 mg CuO Found %: Cu 34.00, 34.30. $C_6H_6ON_2Cu$. Computed % Cu 34.23.	4.553 mg substance: 1.700 mg CuO. 4.398 mg substance: 1.140 mg CuO. Found %: Cu 20.53, 20.71. $(C_6H_7ON_2)_2Cu$. Computed %: Cu 20.52.
Analysis of the oxime	–	3.055 mg substance: 0.608 ml N_2 (17°, 733 mm). 4.570 mg subs: 0.924 ml N_2(18°, 727 mm). Found %: N 22.60, 22.69 $C_6H_6ON_2$. Computed %: N 22.74.

Analysis of the oxime of 2-butyrylpyrrole (m.p. 119°):

3.960 mg substance: 0.638 ml N_2 (26°, 751 mm). Found %: N 18.30. $C_8H_{12}ON_2$. Computed %: N 18.42.

Analysis of the Cu salt of the oxime of 2-butyrylpyrrole:

4.215 mg substance: 0.920 mg CuO. Found %: Cu 17.44. $[C_8H_{11}ON_2]_2Cu$. Computed %: Cu 17.58.

Oximes of 2-Benzoylpyrrole

Isomer with a m.p. of 147°. Analysis of the oxime's Cu salt:

3.750 mg substance: 1.188 mg CuO. 3.025 mg substance: 0.954 mg CuO. Found %: Cu 25.32, 25.19. $C_{11}H_8ON_2Cu$. Computed %: Cu 25.66.

Isomer with a m.p. of 58°. Analysis of the oxime:

2.840 mg substance: 0.377 ml N_2 (18°, 730 mm). Found %: N 14.95. $C_{11}H_{10}ON_2$. Computed %: N 15.05.

SUMMARY

When 2-pyrrolaldehyde is carefully oximated, it yields two stereoisomeric oximes. The syn form is not very stable, with a m.p. of 70-71°, and is readily isomerized to the anti form with a m.p. of 164°. Their configuration has been demonstrated by the preparation of the characteristic copper salts (Chugaev method). 2-Acetylpyrrole forms two stereoisomeric ketoximes: anti-methylpyrryl ketoxime (m.p. 145°), which is less stable; and syn-methylpyrryl ketoxime (m.p. 82°). Their configuration has been determined by the copper-salt method. Both forms of the oximes of 2-acetylpyrrole yield methyl pyrrolcarboxamide when treated with phosphorus pentachloride. The oxime of 2-butyrylpyrrole has been prepared as a single isomer (m.p. 119°), having the structure of syn-propylpyrryl ketoxime. Oximation of 2-benzoylpyrrole yields a mixture of the stereoisomers: syn-phenylpyrryl ketoxime (m.p. 58°), which is less stable; and anti-phenylpyrryl ketoxime (m.p. 147°) which is more stable.

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SULFONATION AND SULFO ACIDS OF ACIDOPHOBIC COMPOUNDS

XIII. THE SULFONATION OF CYCLOPENTADIENE

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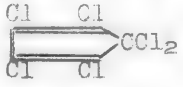
In our previous paper [1] we showed that pyridine sulfotrioxide – a sulfonating agent for acidophobic compounds [2] – sulfonates α-phenylbutadiene to α-phenylbutadienesulfonic acid. We have applied the sulfonation method we have developed to cyclopentadiene. As we know, cyclopentadiene polymerizes extremely easily. It is spontaneously transformed into dicyclopentadiene at ordinary temperature. The rate of polymerization rises rapidly when heat is applied. This sensitivity of the diene to acids is so great that even a minute quantity of acid produces rapid tarring. When cyclopentadiene is brought into contact with concentrated nitric or sulfuric acid, an explosion results [3]. In addition to the typical addition reactions at the double bonds, some substitution reactions are also known for cyclopentadiene. By the use of sodium hypochlorite or hypobromite, cyclopentadiene can be exhaustively halogenated, yielding the respective substituted



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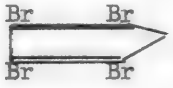


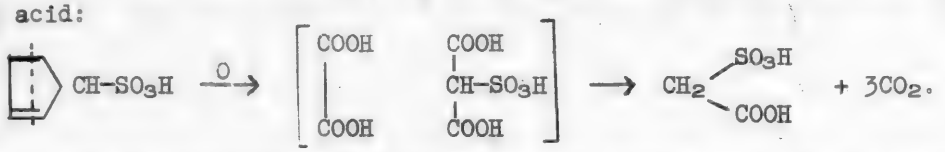
[4].

In 1900 Thiele [5] noticed that in an alkaline medium cyclopentadiene reacted with phenyldiazonium chloride without the evolution of any gas, and with the formation of a black precipitate. Thiele did not investigate the structure of the resulting compound. This reaction was utilized by one of the present authors and L.A.Solokhin [6] to make a quantitative determination of cyclopentadiene in mixtures.

Cyclopentadiene has not been sulfonated hitherto. We sulfonated it by heating it with pyridine sulfotrioxide in a dichloroethane solution. The sulfo mass took on a dark color even at room temperature. The sulfo melt turned black within 3-4 hours when heated to 80-100°. Treating the sulfonation product with an excess of baryta water enabled us to recover a dark brown substance of indeterminate composition, which exhibited a barium-ion reaction in aqueous solutions. The reaction clearly entailed tarring. As we know, when oxygen is present and particularly when heated, cyclopentadiene yields a diperoxide of cyclopentadiene plus other oxidation and tarring products [7]. That is why we performed the sulfonation of cyclopentadiene in a nitrogen atmosphere, with no oxygen present. Under these conditions much less tarring was observed. We succeeded in choosing reaction conditions that provided fairly high yields of the cyclopentadienesulfo acid. We conducted the process at 50-80° for 4-6 hours. The sulfonation product looked like a viscous, dark-brown mass. Treatment with concentrated ammonia and a baryta solution produced a 42% yield of the barium salt of the monosulfonic acid. The Ba, Na, and K salts

are crystalline substances that dissolve readily in water.

The cyclopentadiene sulfonic acid differs from sulfo acids of the $C{=}CH{-}SO_3H$ type in its behavior toward oxidants. Sulfo acids with a vinylic sulfo group readily split off their sulfo group as sulfuric acid when reacted with permanganate [1,8]. Solutions of salts of cyclopentadienesulfonic acid decolorize permanganate, but no sulfuric acid is found even after they have been boiled for a long time with this oxidizing agent. There is no doubt that the sulfo group is not attached to a double bond, but rather to the methylene group. This is confirmed experimentally by the fact that a sulfoacetate was found in the oxidation products. The only way in which it could have been formed is by the oxidation of cyclopentadiene-(1,3)-sulfonic-5 acid:



There are two ways of resolving the question of the manner in which the sulfo group enters the cyclopentadiene molecule. As we know, the hydrogen atoms of the methylene group resemble somewhat the hydrogen in a hydroxyl group, which is replaced by metals when reacted with alkali metals and organomagnesium compounds. When reacted with alcohols, pyridine sulfotrioxide yields sulfates [9]. Hence, the direct introduction of SO_3 into the methylene group is quite conceivable. On the other hand, when we compare the structure of cyclopentadiene with that of furan, pyrrole, thiophene, or divinyl, it may be asserted by analogy [2] that sulfonation takes place at the edge of the conjugated system, i.e., the first step is the formation of cyclopentadiene-(1,3)-sulfonic-1 acid. But the high mobility of the hydrogen atoms results in a rearrangement into a more stable form.

EXPERIMENTAL

Cyclopentadiene. This was produced by depolymerizing dicyclopentadiene by the method described by Stobbe and Reuss [7]. The resulting hydrocarbon had these constants: B.p. 39.5°; d_4^{20} 0.8047; n_D^{18} 1.4473, which agreed with the data in the literature.

Sulfonation. 32 g (0.2 mol) of pyridine sulfotrioxide was placed in a glass tube, and the tube was then filled with approximately 25 ml of dichlorethane to displace the air in it. Then 6.6 g (0.1 mol) of freshly distilled cyclopentadiene was added. The air in the tube was displaced by nitrogen, and the tube was sealed. The sulfo mixture was heated to 50-80° for 6 hours. The contents of the tube turned into a viscous mass that was nearly black. No pressure or odor of sulfur dioxide was noticed when the tube was opened. The sulfo product was dissolved in 40 ml of concentrated ammonia. The aqueous ammonia layer was washed several times with benzene and treated with 65 g of baryta. The dark filtrate exhibited a reaction for the barium ion and highly unsaturated properties. It was evaporated until the solution was saturated and then precipitated with methanol. The precipitated barium salt contained a trace of tarry substances. Triple reprecipitation yielded 9 g (42%) of the pure salt, corresponding to a monosulfonic acid.

3.039, 3.758 mg substance: 1.667, 2.096 mg $BaSO_4$. Found %: Ba 32.29, 32.82. $(C_5H_5O_3S)_2Ba$. Computed %: Ba 32.12.

The potassium salt was prepared from the barium one by precipitation with a solution of potassium sulfate.

3.384, 3.279 mg substance: 3.611, 1.578 mg K_2SO_4. Found %: K 21.37, 22.06. $C_5H_5O_3SK$. Computed %: K 21.22.

Oxidation of a salt of cyclopentadiene-(1,3)-sulfonic-5 acid and isolation of sulfoacetic acid as a salt. 12.5 g potassium permanganate, finely ground, was added in small batches to a solution of 2.8 g of the potassium salt in 80 ml of water. The solution was quickly decolorized, while it warmed up. Toward the end of the reaction the mixture was heated over a water bath. After the manganese dioxide had been filtered out, a solution of barium chloride was added to the filtrate until no more white precipitate settled out. The precipitate was treated by heating it with dilute acetic acid to dissolve the barium carbonate and oxalate. The residue contained the difficultly soluble barium sulfoacetate. (At 20°, 100 g of water dissolves 0.2668 g of barium sulfoacetate.) The salt was recovered in its pure state by hot extraction with water. Analysis of its barium content indicated that it was a monohydrate of barium sulfoacetate.

5.262 mg substance: 4.201 mg $BaSO_4$. Found %: Ba 46.98. $C_2H_2O_5SBa \cdot H_2O$. Computed %: Ba 46.80.

The salt was boiled with benzene to remove the water of crystallization.

Determination of barium in the anhydrous salt: 4.610 g subs: 4.031 mg $BaSO_4$. Found %: Ba 50.28. $C_2H_2O_5SBa$. Computed %: Ba 49.86.

SUMMARY

1. Pyridine sulfotrioxide is a suitable agent for sulfonating cyclopentadiene.

2. Cyclopentadiene-(1,3)-sulfonic-5 acid has been prepared for the first time as its barium salt.

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SULFONATION AND SULFO ACIDS OF ACIDOPHOBIC COMPOUNDS

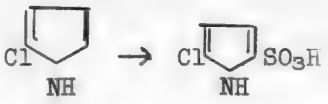
XIV. THE SULFONATION OF 2-CHLOROPYRROLE AND 2-BENZENEAZOPYRROLE

A. P. Terentyev and L. A. Yanovskaya

In our previous reports we have described a method that makes it possible to prepare the sulfo acids of pyrrole and of some of its derivatives [1]. The sulfonating agent employed is the addition product of sulfur trioxide and pyridine: pyridine sulfotrioxide. In the present paper, we report on the further application of our method to the sulfonation of particularly unstable and acidophobic pyrrole compounds. As we know, the introduction of ortho and para orienting substituents into the pyrrole ring makes the latter extremely sensitive. The simplest oxypyrroles, for instance, are unknown. All efforts to prepare 2-aminopyrrole, as by reducing azo compounds [2], have proved unavailing. The aminopyrrole that results is immediately polymerized to a tarry substance. One of the more highly stable of the halogen derivatives is 2-chloropyrrole, but it, too, decomposes within 2-3 hours at room temperature [3]. 2-Bromopyrrole is formed only at low temperatures (-20-25°) [4]. The azo derivatives of pyrrole are also relatively unstable [5]. This explains in part why there are practically no papers in the literature on simple substitution reactions for pyrroles with positive substituents, with the single exception of a paper by Mazzara [6] on the exhaustive bromination of 2-chloro-, 2,5-dichloro-, and 2,3,5-trichloropyrrole in order to establish the structure of these compounds. Pyridine sulfotrioxide is a gentle enough sulfonating agent, and the entrance of a sulfo group stabilizes the pyrrole ring. This led us to attempt to employ pyridine sulfotrioxide to introduce a sulfo group into such unstable derivatives as 2-chloropyrrole and 2-benzeneazopyrrole, which are, however, fairly accessible.

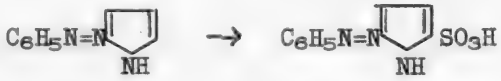
2-Chloropyrrole. This was prepared by the Mazzara method [3]: reacting pyrrole with sulfuryl chloride; it decomposed very rapidly indeed. We were able, however, to sulfonate it with pyridine sulfotrioxide in the course of four hours in an ether solution at 60-70° in an atmosphere of nitrogen. The process was accompanied by considerable tarring. The sulfo mass was completely black. Heating the product of the sulfonation reaction with barium carbonate over a water bath yielded a filtrate that contained chlorine and barium ions. The chlorine ion was removed by precipitation with silver sulfate. The resulting solution was evaporated and then precipitated with an alcohol-ether mixture. The barium salt recovered split off a chlorine ion when boiled, or even when allowed to stand, with dilute nitric acid. The chlorine content of the salt was lower than the computed value, however. We subjected the salt to fractional crystallization from a water-alcohol mixture. This enabled us to isolate the pure barium salt of 2-chloropyrrolesulfonic-5 acid. This structure of the salt was demonstrated by oxidizing it with a chromic acid

mixture, the only product formed being maleinimide, which was identified by its m.p. of 92-93°. The yield of the pure salt was 40%. Hence, the sulfonation process was as follows:



The appearance of a chlorine ion in the reaction mixture after the sulfo mass had been treated with barium carbonate may be explained in two ways. Either partial dismutation of the 2-chloropyrrole takes place during the sulfonation process, liberating chlorine and forming dichloropyrrole, which turns into tar, and pyrrole, which is sulfonated, yielding the respective pyrrolesulfonic acid (lowering the percentage of chlorine and raising the percentage of barium in the salt initially recovered); or the 2-chloropyrrolesulfonic-5 acid is partially saponified when treated with barium carbonate. This latter is not very likely, however, inasmuch as the pure salt does not split off a chlorine ion when boiled with barium carbonate. The barium salt of 2-chloropyrrolesulfonic-5 acid is readily soluble in water and fairly soluble in a water-alcohol mixture. It is hydrolyzed vary easily by boiling with 15% hydrochloric acid, sulfur dioxide being evolved. Alkaline hydrolysis by a solution of sodium hydroxide results in splitting off a chlorine ion. The action of bromine water in the cold splits off the sulfo group as barium sulfate.

2-Benzeneazopyrrole was prepared by the Fischer and Hepp Method [7], combining pyrrole with phenyldiazonium chloride. It is sulfonated by pyridine sulfotrioxide in an ether solution during 8 hours at 70-80°, again with considerable tarring. The isolated barium salt of 2-benzeneazopyrrolesulfonic acid was yellow and dissolved in water and in alcohol, turning the solution orange-red. The salt is quite stable in the dry state and in solutions. The yield of the salt was about 50%. Hydrolysis is readily effected, sulfur dioxide being evolved. The sulfo group is split off completely when the salt is oxidized with chromic acid mixture, i.e., the acid has the structure of 2-benzeneazopyrrolesulfonic-5 acid. The sulfonation process may be pictured as follows:



This pyridine sulfotrioxide proves to be a suitable sulfonating agent in these instances as well. As with 2-methylpyrrole, the sulfo group is in the second α-position.

EXPERIMENTAL

Sulfonation of 2-chloropyrrole. The 2-chloropyrrole was prepared by the Mazzara and Borgo method [3]: adding a precisely calculated quantity of an ether solution of sulfuryl chloride drop by drop, with chilling to 0°, to a highly diluted solution of pyrrole in absolute ether. 2-Chloropyrrole is highly unstable, turning into a black tar within 2 to 3 hours, even when kept in a nitrogen atmosphere in the cold (0°). 2.5 g of 2-chloropyrrole dissolved in ether was sulfonated in a nitrogen atmosphere by 5.45 g of pyridine sulfotrioxide in a sealed tube during four hours at 60-70°. The resulting viscous black mass was heated with a suspension of barium carbonate over a water bath until all the pyridine had been eliminated. Then the mass was extracted with boiling water. The filtrate exhibited a chlorine-ion reaction, so that it was cautiously treated with a solution of silver sulfate until all the chlorine had been precipitated. The deposit was filtered out, and the solution was evaporated to small volume and then precipitated with an alcohol-ether mixture. The resulting barium salt contained less chlorine and more barium

than was called for in a salt of chloropyrrolesulfonic acid. The salt was purified by double fractional crystallization from a water-alcohol mixture. 2.5 g (40% yield) of the pure salt was obtained.

5.991 mg substance: 2.817 mg $BaSO_4$. 5.260 mg substance: 2.485 mg $BaSO_4$.
0.1070 g substance: 0.0205 g AgCl. 0.1015 g substance: 0.0191 g AgCl.
Found %: Ba 27.67, 27.80; Cl 14.25, 14.26.
$(C_4H_3O_3NSCl)_2Ba$. Computed %: Ba 27.55; Cl 14.22.

Oxidation of the barium salt with chromic acid mixture. 1 g of the barium salt of chloropyrrolesulfonic acid was added in small batches to a solution of 1.2 g of chromic anhydride and 3.5 g of concentrated sulfuric acid in 20 ml of water, heated to 50°. The mixture was kept at this temperature for 25 minutes, after which it was set aside to stand overnight. The next day the mixture was extracted 15 times with small batches of ether. The extract was desiccated with calcium chloride and evaporated in air. This yielded about 30 mg of slightly colored crystals of maleinimide. The m.p. was 92-93° after recrystallization from ethyl acetate, which agrees with the data in the literature [8]. The extraction residue was neutralized with barium carbonate, and all the soluble salts were extracted with boiling water. The extract was evaporated to dryness and the resulting residue was tested for sulfur. It contained no sulfur, i.e., all the sulfo group had been split off during oxidation. This proves that the initial substance had the structure of 2-chloropyrrolesulfonic-5 acid.

Barium salt of 2-chloropyrrolesulfonic-5 acid. The salt is readily soluble in water and in a water-alcohol mixture, but is insoluble in ether or other organic solvents. It is hydrolyzed by boiling it for 15-20 minutes with 15% hydrochloric acid, sulfur dioxide being evolved. Bromine water is decolorized by a salt solution in the cold, barium sulfate being formed. Heating the salt with dilute nitric acid or letting a nitric acid solution of the salt stand for a long time (2-3 hours) splits off a chlorine ion. Boiling the salt for a short time with a 20% sodium hydroxide solution likewise splits off a chlorine ion.

Sulfonation of 2-benzeneazopyrrole. The 2-benzeneazopyrrole was prepared by the Fischer and Hepp method [7]: combining an alcoholic solution of pyrrole in the cold with phenyldiazonium chloride in acetic acid. M.p. 62-63° (from alcohol), which agrees with the figure given in the literature. 1.71 g of 2-benzeneazopyrrole in ether solution was sulfonated in a nitrogen atmosphere with 4.77 g of pyridine sulfotrioxide by heating to 70-80° for 8 hours. The dark brown mass was heated with an aqueous suspension of barium carbonate until all the pyridine had been eliminated. The residue was extracted with hot water. The extract was evaporated and then precipitated with an alcohol-ether mixture. This yielded 1.60 g of a salt, the barium content of which corresponded to that of a monosulfo acid (50% yield).

5.550 mg substance: 2.028 mg $BaSO_4$. 5.317 mg substance: 1.935 mg $BaSO_4$.
Found %: Ba 21.50, 21.42. $(C_{10}H_8O_3N_3S)_2Ba$. Computed %: Ba 21.54.

The barium salt of 2-benzeneazopyrrolesulfonic-5 acid is yellow and readily soluble in water and methanol, turning the solutions orange red. When bromine water reacts with a salt solution in the cold, it splits off barium sulfate. The salt is hydrolyzed by boiling it for 15 20 minutes with 15% hydrochloric acid, sulfur dioxide being evolved.

Oxidation of the barium salt with chromic acid mixture. 0.8 g of the salt was oxidized as specified above. No substances containing sulfur were found in the oxidation products, i.e., all the sulfo group was split off. Hence, the structure of the salt is that of 2-benzeneazopyrrolesulfonic-5 acid.

SUMMARY

1. It has been shown that pyridine sulfotrioxide may be employed to sulfonate 2-chloropyrrole and 2-benzeneazopyrrole.

2. 2-Chloropyrrolesulfonic-5 acid and 2-benzeneazopyrrolesulfonic-5 acid have been prepared for the first time, as their barium salts.

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*See CB translation p. 487 ff.

THE STRUCTURE OF PROTEIN MICROMOLECULES

V. THE ACTION OF PHOSPHORUS PENTACHLORIDE UPON DIKETOPIPERAZINE

N. I. Gavrilov, R. G. Petrova and N. A. Poddubnaya

In our preceding report, we specified certain conditions that must be met in the preparation of dichlorodihydropyrazine from diketopiperazine and phosphorus pentachloride. Our subsequent research has shown that it is not always possible to secure the dichloride even when the specified conditions are observed. We were unable to find the conditions under which nothing but dichlorodihydropyrazine would be produced. Often, instead of getting dichlorodihydropyrazine, we recovered a substance containing phosphorus and representing a phosphorus compound of diketopiperazine.

This circumstance forced us to make a detailed investigation of the conditions governing the formation of dichlorodihydropyrazine when diketopiperazine is reacted with phosphorus pentachloride.

EXPERIMENTAL

Maintaining the reaction conditions that we had evolved for the synthesis of dichlorodihydropyrazine, in some instances we secured compounds that had the same crystalline form as the dichloride, but did not melt at 80-90°; they contained phosphorus and, in contrast to dichlorodihydropyrazine, they turned red when treated with picric acid and soda.

1. Investigation of the Phosphorus Compound

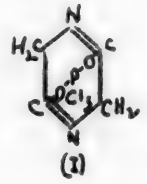
(Description of the anomalous reaction)

a) In carbon tetrachloride. 0.5 g of diketopiperazine, carefully pulverized in a porcelain mortar with 4 g of phosphorus pentachloride, was transferred to the apparatus described in our preceding paper [1], and the mixture was rapidly heated after 40 ml of anhydrous carbon tetrachloride had been added. The reaction was carried out for 5 hours, the carbon tetrachloride being kept at a gentle boil. After the mixture had cooled, the precipitate was filtered out in the same apparatus, protecting it against atmospheric moisture, and then washed 3 or 4 times with anhydrous carbon tetrachloride. The crystals that remained in the apparatus were separated from the solvent by evacuating the apparatus. The resulting light-yellow crystals decomposed at about 200° (on the thermometer). Visible as prisms under the microscope, sometimes bunched into rosettes, they contain phosphorus and exhibit a diketopiperazine reaction. When exposed to the air on a glass slide, the crystals decompose within a day, forming crystals of a dipeptide, constituting a characteristic coordination compound of copper.

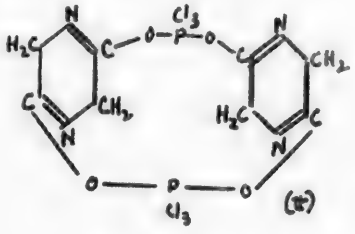
Found %: N 10.35 (Kjeldahl method); Cl 41.5; P 11.8 (Tsintsiadze method); $(C_4H_4O_2N_2Cl_3P)_n$. Computed %: N 11.2; Cl 42.6; P 12.4.

The substance contained one atom of phosphorus and three atoms of chlorine per two atoms of nitrogen, and might have the structure of an ester of trichlorophosphoric acid and the enol of diketopiperazine or an amide of the sameacid and diketopiperazine.

Microscopic examination of the crystals disclosed a small quantity of crystals of unreacted diketopiperazine, which was reflected in the results of analysis. We were unable to recrystallize the substance. Nor were we able to determine its molecular weight, owing to the insolubility of the phosphorus compound.

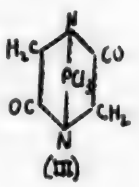


(I)

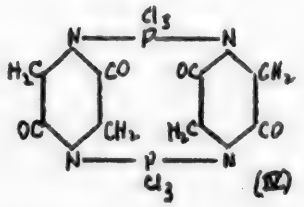


(II)

b) In benzene. 1 g of diketopiperazine, carefully pulverized in a mortar with 8 g of phosphorus pentachloride, was heated in our apparatus with 40 ml of benzene. The boiling that set in quickly was accompanied by the copious evolution of hydrogen chloride, the solution turning yellos. All the ingredients had dissolved after 20 minutes had elapsed; the solution was then refiltered while hot into a similar apparatus. The copious precipitate that settled out after standing for an hour was filtered out in the same apparatus and washed with carbon tetrachloride, the traces of solvent being removed by evacuation. The substance fused at 160-170° with decomposition. It contained phosphorus. Under the microscope the crystals had the shape of long needles, entirely identical to those of dichlorodihydropyrazine. The yield was 0.75 g.



(III)



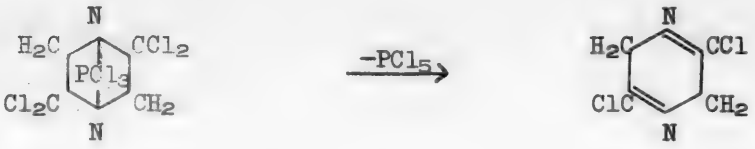
(IV)

They dissolved when treated with very cold water. The substance does not titrate on the Sorensen scale – it contains no amino nitrogen.

Found %: N 10.1 (Kjeldahl); Cl 42.3 (Volhard); P 12.5 (Tsintsiadze): C 19.56, 19.47; H 4.01, 3.95. $(C_4H_4O_2N_2Cl_3P)$. Computed %: N 11.2; Cl 42.6; P 12.4: C 19.24; H 1.6.
We were unable to determine the molecular weight.

Behavior with chilled methanol. Solid carbon dioxide was added to absolute methanol, and when the temperature was low enough, 100 mg of the test chloride was added. When the temperature had reached 10-15°, the remaining deposit was suction-filtered out and washed with chilled alcohol and ether (weight 50 mg). Its melting point (316°) and its crystalline form indicated that it was diketopiperazine. The ease of this alcoholysis indicates that the unknown substance cannot be an amide of trichlorophosphoric acid and diketopiperazine; it is more likely to be an ester of trichlorophosphoric acid and the enol of diketopiperazine.

Analysis of the resultant chloride. To make sure that the substance we had prepared was not an amide, we reacted it with oxalyl chloride [2], which should have chlorinated the carbonyl group of the N-phosphorylated diketopiperazine, splitting of PCl_5 and forming dichlorodihydropyrazine.



Such a reaction did not take place.

Action of oxalyl chloride upon the resultant phosphorus compound of diketopiperazine. 11 g of the phosphorus compound was treated for 5 hours with 1.4 ml of oxalyl chloride in a small quantity of ether. The crystals retained their shape and contained phosphorus. The ether was driven off in vacuum, a considerable quantity of oxalyl chloride and carbon tetrachloride was added, and heating was continued for another 6 hours. The unchanged crystals were filtered out, washed with the solvent in the same vessel, from which the solvent was then removed by evacuation. Analysis and the crystalline form indicated that the substance had remained unchanged.

Found %: N 10.5 (Kjeldahl); Cl 39.9 (Volhard); P 11.27 (Tsintsiadze); C 18.4; H 2.7. ($C_4H_4O_2N_2Cl_3P_1$). Computed %: N 11.2; Cl 42.6; P 12.4; C 19.24; H 1.4.
We were unable to determine the molecular weight.

If the substance were acylated diketopiperazine (with trichlorophosphoric acid), the action of the free ester of glycine [3] upon it in ether solution should result in the formation of:

1) An ester of the amidine of glycine, or

2) Diketopiperazine and an N-phosphorylated ester of glycine.

0.5 g of the phosphorus compound was reacted with the free ester of glycine in absolute ether. The mixture was stirred in the flask (which was deeply chilled) with a stirrer, while an excess of the free ester of glycine was added a little at a time. As the reaction proceeded, the precipitate was re-formed; it was suction-filtered and washed with absolute ether.

Analysis of the precipitate. It contained no phosphorus. The precipitate was treated with a small amount of absolute methanol, most of the precipitate dissolving. The 15-20 mg of precipitate that did not dissolve proved to be diketopiperazine.

After having been precipitated with an alcoholic solution of ether, the isolated precipitate was identified by its melting point and by a Sorensen test for nitrogen content as the hydrochloride of the glycine ester.

The ether solution contained phosphoric acid and displayed an anhydride reaction with picric acid. After the ether had been driven off, a small quantity of diketopiperazine crystals settled out of the residual oil. The crystals were filtered out, and the oil was redissolved in ether, hydrogen chloride then being passed through the solution. The precipitate was found to contain nothing but the hydrochloride of the glycine ester. The ether solution contained phosphoric acid.

It may be concluded from the foregoing experiments that: 1) the phosphorus compound remained unchanged when reacted with oxalyl chloride, which indicates that the phosphoric acid group cannot be attached to the nitrogen in the diketopiperazine.

2) According to Bergmann and Brunner [4], reaction with acylated amines ought to produce the respective amidine or acylated amino acid, in this case, a phosphorylated acid. We did not secure these compounds. This excludes the possibility that this compound has the structure of an amide or of a phosphoric ester of the enolic form of diketopiperazine.

Thus, we were unable to guess the structure of the phosphorus compound we had secured. We turned to a study of the optimum conditions for preparing dichlorodihydropiperazine. We investigated the solvents in which the chlorination by phosphorus pentachloride takes place, and also endeavored to convert diketopiperazine into an active state in one way or another.

2. Investigation of the Reaction Conditions Governing the Preparation of 2,5-Dichlorodihydropiperazine

Solvents. It is sometimes possible to perform the reaction resulting in the formation of 2,5-dichlorodihydropiperazine in benzene, but the chloride yield is much lower than when the reaction is performed in carbon tetrachloride, and the resulting compound is somewhat colored, it being impossible to eliminate the color owing to its insolubility in indifferent solvents.

Both the phosphorus compound and the dichloride are secured in toluene, but the latter is considerably tarred and its yield is negligible.

The reaction did not take place in pentane or cyclohexane, evidently because of the complete insolubility of both reagents.

In iso-octane, a substance that quickly tarred was produced within 15-20 minutes of the onset of the reaction, but nonetheless the 44.2% of chlorine in the crude product indicated that the dichloride had been formed.

The reaction did not occur at all in light gasoline (50-70°).

Chlorination in n-hexane (69°) yielded a substance with a m.p. of 120-122°. The substance resinifies very quickly in air and exhibits the biuret reaction directly.

In acetyl chloride, the reaction resulted in the formation of a phosphorus compound. A mixture of acetyl chloride and carbon tetrachloride yielded similar results.

We also tested the chlorination of diketopiperazine with phosphorus pentachloride in carbon tetrachloride to which quinoline had been added. The latter, as a base, ought to diminish the acidity of the solution and thus prevent the formation of a phosphorylated compound of diketopiperazine. Tests made with quinoline present in the solution, however, resulted in the formation of a somewhat resinified oil, which contained a large percentage of the original diketopiperazine. Investigation of the above-mentioned solvents thus led us to conclude that the chlorination reaction cannot be made to produce dichlorodihydropiperazine merely by choosing the solvent suitably.

Preliminary treatment of the diketopiperazine. Diketopiperazine, as the major component in the chlorination reaction, ought to influence the course of the chlorination reaction. (All the preceding experiments had been performed with a diketopiperazine that had been prepared by the Fischer method and thoroughly heated to 150° for 5 days). We therefore ran a series of experiments using a modification of the preliminary treatment of the diketopiperazine.

1) The diketopiperazine was dissolved in boiling aniline, as specified by Abderhalden [5]. The crystals of diketopiperazine that settled out upon cooling were suction filtered and washed repeatedly with alcohol and ether. The desiccated crystals fused at 274°. Contrary to Abderhalden's assertion, diketopiperazine prepared in this manner did not react with permanganate. Chlorination with phosphorus pentachloride resulted in formation of the phosphorus compound as well as dichlorodihydropiperazine.

The diketopiperazine prepared in this manner did not react at all (5 hours) with phosphorus trichloride in carbon tetrachloride, which indicates that it is not the enolic form of diketopiperazine.

2) Bergmann [8] prepared aceturic acid and diketopiperazine by reacting diacetyldiketopiperazine with the sodium salt of glycine in water.

Bergmann's equation and our experiments (Report 7) agree that the diketopiperazine thus prepared must be in the keto form.

Diacetyldiketopiperazine, produced by the Friedman method, was treated with the sodium salt of glycine in water, as specified by Bergmann. The resulting absolutely pure diketopiperazine fused at 316° and contained 24.34% nitrogen by the Kjeldahl test (24.5% theoretically). Reacting it with phosphorus pentachloride under the usual conditions yielded the phosphorus compound.

3) The diketopiperazine was irradiated with an uviol lamp for 12 hours in a quartz flask (distance = 20 cm). Chlorination under the usual conditions resulted in formation of the phosphorus compound.

4) Crystallization of diketopiperazine from alcohol.

In the light of E.Fischer's observations on the reaction of glycine, recrystallized from alcohol, with phosphorus pentachloride, which produced a high yield of the chloride of the amino acid, we tried to precipitate diketopiperazine with alcohol. A saturated solution of diketopiperazine in water was precipitated with hot absolute alcohol until the precipitate was completely formed. After the solution had cooled, the diketopiperazine was filtered out and dried for 30 hours at 110°. The diketopiperazine thus prepared produced the phosphorus compound when reacted with phosphorus pentachloride.

5) We were unable to prepare diacetyltetrachloropiperazine or dichlorodihydropiperazine by reacting diacetyldiketopiperazine with phosphorus pentachloride for 4 hours in carbon tetrachloride. The diacetyldiketopiperazine was recovered from the solution unchanged, except for some slight tarring.

We were able to secure a minute amount of crystals of dichlorodihydropiperazine, containing no phosphorus and fusing at 70°, by reacting diacetyldiketopiperazine with phosphorus pentachloride for a long time (24 hours) and then evaporating the resulting solution in vacuum.

SUMMARY

1. In our researches on the effect of the solvent upon the reaction of diketopiperazine with phosphorus pentachloride we were unable to find the optimum conditions for making the reaction produce dichlorodihydropiperazine, even when we changed the nature of the diketopiperazine itself.

2. In the light of our previous experiments, carbon tetrachloride remains the best medium in which to perform the reaction, together with freshly prepared unrecrystallized diketopiperazine or recrystallized diketopiperazine that has been heated to 150° for many hours. But even under these conditions a phosphorus compound of unknown structure is often formed.

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*See CB translation this issue.

THE STRUCTURE OF PROTEIN MICROMOLECULES

VI THE PREPARATION OF SOME DIHYDROPYRAZINE AMIDINES AND THEIR ACYLATION

N. I. Gavrilov and L. N. Akimova

In continuation of our research [1] on the synthesis of amidines consisting of amino-acid derivatives of dihydropyrazine, we have synthesized: the hydrochloride of the 2,5-dimethyl ester of tyrosine-dihydropyrazinamidine, and the hydrochloride of the 2,5-diethyl ester of glycyl-glycine dihydropyrazinamidine. A study has been made of the properties of these substances.

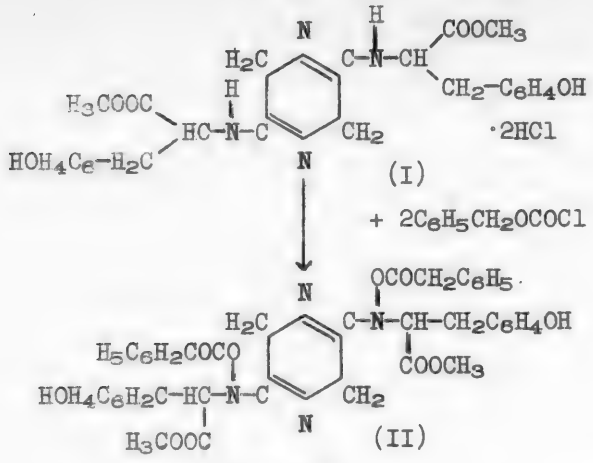
The tyrosinamidine is fairly stable and readily forms carbobenzoxy derivatives. Most important is its property of being wholly untitrated by an alcoholic (96%) alkali (Wilstatter method). This singularity proved to be characteristic of other amidines as well. In contrast to an amidine containing two tripeptide side chains and forming a violet biuret coordination compound, an amidine consisting of dihydropyrazine and two dipeptide side chains does not form a copper coordination compound at all. This case therefore exhibits the same phenomenon that was encountered in the formation of a hexapeptide coordination compound, where two of the amino-acid residues of the hexapeptide cannot form a biuret coordination compound, only four of the amino-acid residues of the molecule participating in the reaction [2]. This may be due to steric hindrance, inasmuch as free dipeptides do form a copper coordination compound.

This property of the amidine points to reciprocal autonomy of its two dipeptides separated by the dihydropyrazine ring.

When we acylated an ester of glycinamidine with carbobenzoxychloride as indicated by Bergmann, the reaction did not result in the formation of an acylated amidine. The only reaction product recovered was carbobenzoxyglycine. This is evidently the result of splitting off alcohol and then carbobenzoxylated glycine from the carbobenzoxylated ester of glycinamidine. The reaction took that turn with MgO present (in water), with pyridine present (in ether, both of these reagents being known to be anhydrous), and with 16% NaOH present, with deep chilling. Under these conditions, diketopiperazine was found and acylated glycine (carbobenzoxyglycine) was recovered.

When the reaction was performed in absolute ether with bicarbonate, no acylated amidine was formed nor did the amidine break down to form acylated glycine.

Acylating tyrosinamidine with carbobenzoxychloride produced a high yield of dicarbobenzoxytyrosinamidine (Equation 1), which is quite stable, owing to the absence of water in the amidine group and the presence of an acyl group in the exo position



Equation 1.

During our research we succeeded in considerably increasing the yield of diketopiperazine during its synthesis over the yield obtained by the Fischer method [3]. This was achieved by substituting ammonia for sodium hydroxide in the reaction of the base with the hydrochloride of the glycine ester. The diketopiperazine thus prepared is easily chlorinated by phosphorus pentachloride under ordinary conditions. When the diketopiperazine is recrystallized from water, it loses its ability to react with phosphorus pentachloride, but regains it after being heated to 150° for 70 to 80 hours in a drying chamber.

There was no difference between the heats of combustion of the reactive and the unreactive diketopiperazine. The reason for the differing reactivity toward PCl_5 of the recrystallized and the unrecrystallized diketopiperazine remained unresolved.

EXPERIMENTAL

Preparation of diketopiperazine. 50 g of methylglycine hydrochloride was mixed with 10 ml of cold water. 27.8 ml of 25% ammonia (insufficiency) was added drop by drop in the course of 45 minutes to the solution with constant mechanical stirring and chilling (to -10° with snow and salt). After this was done, the solution was set aside to stand. The bulk of the diketopiperazine is observed to form within the first 30 minutes. The precipitate was filtered out the next day and carefully washed with cold water and then with methanol. The diketopiperazine was dried in a vacuum exsiccator, after which it did not exhibit a biuret reaction or contain any chlorine. The yield was 13.6 g, or 60% of the theoretical.

Synthesis of dichlorodihydropyrazine. 8 g (1.5 mol excess) of phosphorus pentachloride, carefully comminuted with 1 g of diketopiperazine (prepared as outlined above), was poured on the bottom of a Gavrilov apparatus [4] and 70 ml of anhydrous carbon tetrachloride was cautiously added. The mixture was quickly heated to the boiling point, taking care that no diketopiperazine remained at the bottom of the apparatus while keeping the carbon tetrachloride boiling vigorously. As boiling continued, the phosphorus pentachloride gradually dissolved, and the solution turned pale yellow. Not all the diketopiperazine dissolved. Within half an hour a new precipitate began to settle out, and hydrogen chloride was evolved. The reaction was complete within an hour an a half (no more HCl was evolved). The reaction products were cooled to room temperature. Then the precipitate was filtered out of the solution within the same apparatus, taking care to protect the mixture from atmospheric moisture, and washed 5 times with anhydrous carbon tetrachloride. The substance fused at 83° after having been dried in a vacuum exsiccator. The yield

was 1.25 g, or 95.7% of the theoretical. The phosphorus test was negative.

Synthesis of the Hydrochloride of 2,5-Dimethyl-tyrosine-dihydropyrazineamidine (I)

4.6 g of methyltyrosine hydrochloride, prepared by the Fischer method [5], was dissolved in 25 ml of absolute methanol. 1.5 g of dichlorodihydropyrazine was added in small batches to the solution, which was chilled (with ice) and stirred with a mechanical stirrer. As the addition went on, a new precipitate was seen to form, settling out because of its poor solubility in alcohol. After the reaction was complete, the precipitate was filtered out and washed on the filter with absolute methanol. The substance fused at 132° after being recrystallized from chloroform. Properties: poorly soluble in water, more so in alcohol and acetone, readily soluble in chloroform. It exhibits positive anhydride and Millon's reactions, and negative ninhydrin and biuret reactions. The test for halogen was positive. It is not titrated in the Wilstatter test.

Found %: N 10.32; C 53.17; H 6.09; M (Rast) 536, 539.
$C_{24}H_{30}O_6N_4Cl_2$. Computed %: N 10.35; C 53.23; H 6.15; M 541.

Another test made with chloroform substituted for methanol as the solvent yielded no results at all. The reaction products included methyltyrosine hydrochloride and a chloride of a dipeptide ester (glycyl-glycine), resulting from the breakdown of the dichlorodihydropyrazine, together with diketopiperazine

Carbobenzoxy Derivative of Tyrosinamidine (II)

0.5 g of tyrosinamidine and 0.3 g of carbobenzoxychloride were dissolved in 30 ml of chloroform. This solution, chilled extremely well (snow + salt), was added to an equally well chilled bicarbonate solution (0.6 g of $NaHCO_3$ in 30 ml of water) The mixture was stirred with a mechanical stirrer. The neutral solution was filtered through a paper filter and extracted three times with chloroform. The chloroform solution was desiccated and then evaporated in vacuum without heating, the residue being recrystallized from benzene and dried in a vacuum exsiccator. M.p. 122°. The yield was 0.5 g, i.e., 75.9% of the theoretical.

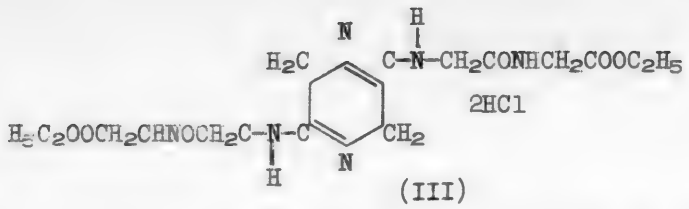
Found %: N 7.53, 7.57; C 64.98; H 5.37; M (Rast) 729.
$C_{40}H_{40}O_{10}N_4$. Computed %: N 7.61; C 65.22; H 5.43; M 736.

Hydrochloride of the 2,5-Diethyl Ester of Glycyl-glycine dihydropyrazinamidine (III)

3.9 g of the hydrochloride of the ethyl ester of glycyl-glycine, prepared by the Fischer method [8], was dissolved in 15 ml of absolute methanol. 1.5 g of dichlorodihydropyrazine was added to the solution with chilling (ice) and stirring with a mechanical stirrer. When the reaction was over, a small amount of diketopiperazine (a few mg) was filtered out of the solution. The transparent solution was precipitated with absolute ether. The first thing to settle out was an oil. The solution was decanted from the latter. The oil cyrstallized after standing overnight. Inasmuch as it contained phosphorus (test with ammonium molybdate), it was not analyzed. Absolute ether was added to the solution that had been decanted from the oil. The resulting precipitate was filtered out and washed with absolute ether. The substance fused at 156° after having been dried in a vacuum exsiccator. Properties: readily soluble in water and in alcohols, poorly soluble in chloroform, acetone, and benzene. When heated for a long time, it exhibits an anhydride and ninhydrin reaction. No biuret reaction is present at all, with copper or cobalt.

It is not titrated in the Wilstatter test.

Found %: N 17.46; C 40.83; H 5.87; M (Rast) 488.
$C_{18}H_{28}O_6N_4Cl_2$. Computed %: N 17.83; C 40.76; H 5.94; M 471.



(III)

The substance recovered is therefore the hydrochloride of the 2,5-diethyl ester of glycyl-glycine dihydropyrazineamidine.

Endeavor to Prepare the Carbobenzoxy Derivative of Glycinamidine

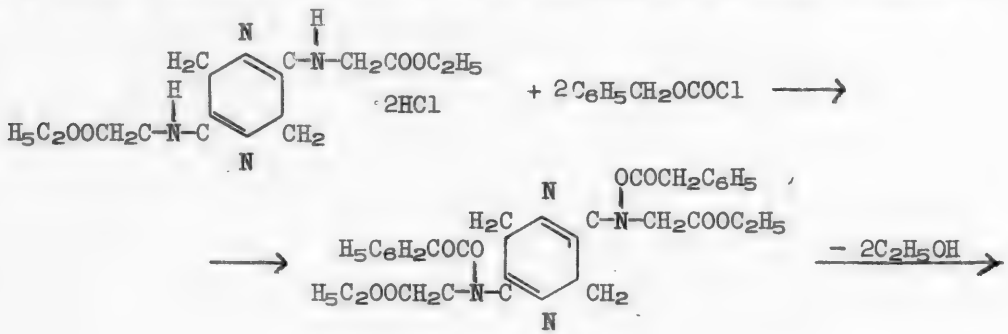
0.5 g of glycinamidine hydrochloride and 0.06 g of MgO were dissolved in water with very intense chilling (snow + salt), and 0.6 g of carbobenzoxychloride was added to the solution a drop at a time with constant mechanical stirring. When the reaction was complete, the medium was neutral, while the bottom of the vessel was covered with oil. After extraction with ether, desiccation of the extract, and driving off the ether, the oil did not crystallize; it proved to be benzyl chloride.

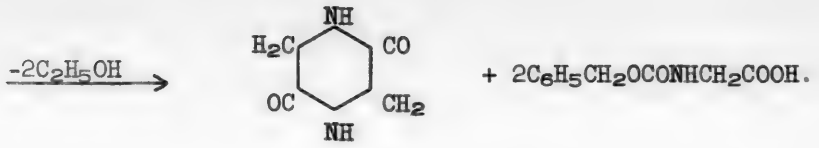
0.12 g $NaHCO_3$ was added to the aqueous solution to eliminate the magnesium. The precipitate that formed when CO_2 was passed through the solution was filtered out. Acidulation with hydrochloric acid caused crystals to settle out; they were filtered out, washed with cold water, and dried in a vacuum exsiccator. M.p. 119.5°. The m.p. given in the literature [7] for carbobenzoxyglycine is 120°.

A similar reaction was carried out with pyridine in absolute ether. The substance recovered fused at 119° and also proved to be the carbobenzoxy derivative of glycine, rather than of the amidine.

Found %: N 6.69 (Kjeldahl). $C_{10}H_{11}O_4N$. Computed %: N 6.70.

The same result was obtained when carbobenzoxychloride was reacted with a solution of glycinamidine in alkali. A small quantity of glycine anhydride was recovered, in addition to the carbobenzoxyglycine. Fearing that the free amidine would be saponified by water in reactions with soda, pyridine, and magnesium oxide, we endeavored to carry out the reaction in absolute ether with $NaHCO_3$ present. No reaction occurred at all, nothing but the amidine (with alcohol) and benzyl alcohol being recovered. The last experiment convinced us that this reaction does not involve decomposition of the amidine, but rather its acylation, for if the amidine were decomposed, we should not find carbobenzoxyglycine in the reaction products, but rather an ester of this compound. And yet we invariably secured carbobenzoxyglycine. As was shown later, the reaction evidently proceeds as follows: the alcohol is split off from the ester group of the acylated amidine, this being followed by a typical Bergmann splitting off of the exo-acylglycine (Equation 2).





Equation 2.

SUMMARY

1. The hydrochloride of the 2,5,dimethyl ester of tyrosine-dihydropyrazinamidine has been synthesized.

2. The hydrochloride of the 2,5-diethyl ester of glycyl-glycine-dihydropyrazinamidine has been synthesized.

3. A study has been made of the carbobenzoxylation of the hydrochloride of the 2,5-dimethyl ester of tyrosine-dihydropyrazinamidine. Its carbobenzoxy derivative has been prepared.

4. A study has been made of the reactions involved in the acylation of the hydrochloride of the 2,5-diethyl ester of glycine-dihydropyrazinamidine.

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THE STRUCTURE OF PROTEIN MICROMOLECULES

VII. SOME TRANSFORMATIONS OF ACYLATED 2,5-DIKETOPIPERAZINES WHEN REACTED WITH AMINO ACIDS AND AMINES

L. N. Akimova and N. I. Gavrilov

In our previous reports [1,2,3] we have shown that:

1. Diketopiperazine may be linked to an amino acid through the carbonyl (2,5) groups of the former and the amino group of the latter. We call this kind of bond an amidine bond.

2. The tripeptides predominate in the protein molecule, constituting 90-95% of the total peptide nitrogen, according to analyses of the Raman spectra of their copper coordination compounds.

3. The model structures we have suggested are fermented by pepsin and intestinal juices, so that they may be considered to have a structure present in natural protein.

4. This has served as a foundation for our suggested structure of the protein micromolecule.

5. Developing our concept of the structure of protein still further, we have advanced two hypothetical structures, which we are now endeavoring to realize.

A. A tripeptide-dihydropyrazine structure (a chain of dihydropyrazine rings, with fringes of tripeptides) (Diagram 1).

B. A polypeptide-dihydropyrazine structure (a chain of polypeptides, linked together by dihydropyrazine rings). (Diagram 2.) In this structure we have the amidine group of our diagram for the protein micromolecule, acylated by the tripeptide residue.

We know [4] that it is rather simple to acylate aromatic and aliphatic (or mixed) amidines. According to Brunner [5], acylated amidines of this sort are prepared by letting amines act directly upon diacyl amides. (Diagram 3).

Other types of links are possible, in addition to the foregoing diagrams for the formation of the macromolecule.*

* A closely related diagram has been recently suggested by M.S. Reznichenko, [illegible] of the Transactions of the 2nd Session of the Medico-Biological Division of the Academy of Medicine.

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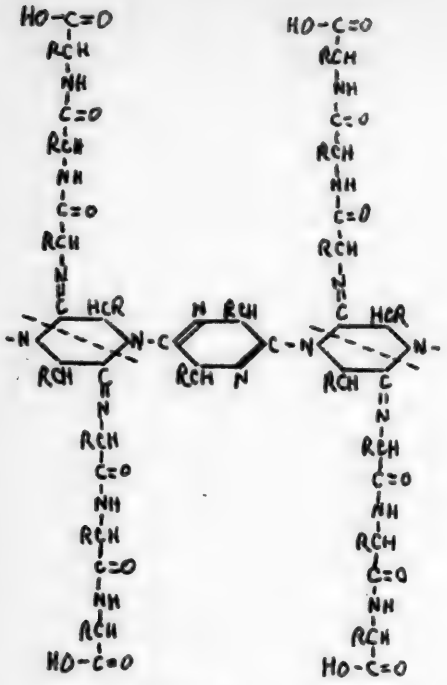

Diagram 1.

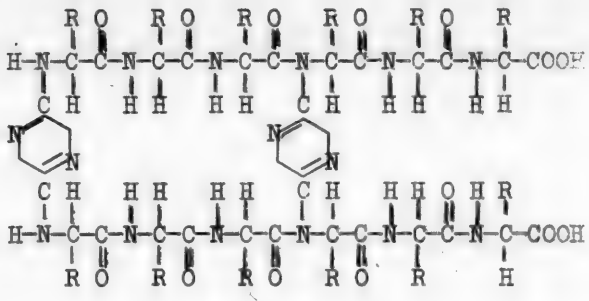

Diagram 2.

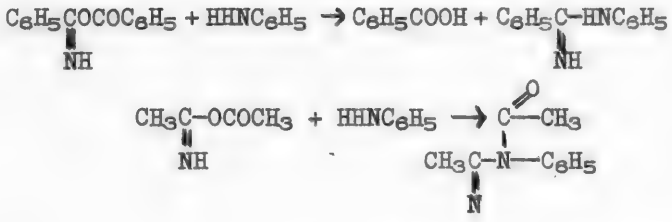

Diagram 3.

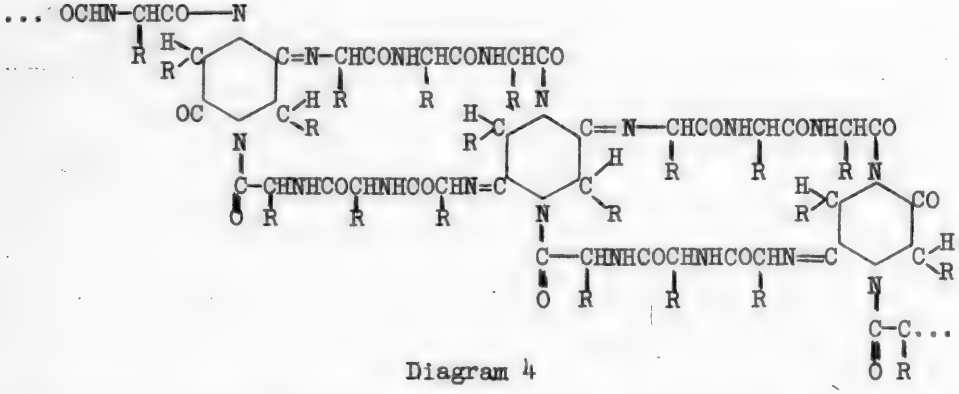

Diagram 4

In this structure the carboxyl group of the tripeptide is linked to the nitrogen of the tautomeric form of the dihydropyrazine, changed into a piperazine ring. This diagram made it necessary to investigate the properties of the acylated (or aminated) compounds of diketopiperazine. E.Abderhalden believed that this type of bond – an aminoacyclic bond – is most probable in the protein molecule between the diketo-

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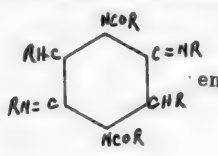
* (cont)

We shall use the following nomenclature for pyrazine amidines [6]:



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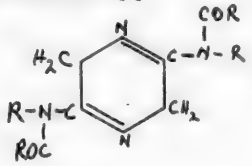

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piperazines and amino acids and the peptides. He endeavored to create it in several researches, but without success, unfortunately [7]. Only in one paper [8] was he able to report the preparation of a compound that possibly was N-leucyl-(glycyl, leucyl) anhydride, but even in this research this structure was not subjected to analysis. Zelinsky and Sadikov, and subsequently Abderhalden, too, isolated anhydrides consisting of 3-5 amino acids from protein hydrolyzates, to which they assigned the structure of cyclopeptides or N-aminoacyl-diketopiperazines. To judge by the later's reactions, they were compounds with the amidine structure we have advanced.

Abderhalden's researches on the synthesis of aminoacylated diketopiperazines were disproved, partly by us, but chiefly in a series of remarkable papers by M. Bergmann and his co-workers. In a joint paper with Kh.N.Lerman [9], we have shown that neither of the procedures for the synthesis of these compounds suggested by Abderhalden – via the cyclization of the esters of tripeptides or the amination of the dichloroacyl derivatives of diketopiperazine – results in an aminoacyl derivative of the latter, but rather in the formation of free diketopiperazine and an amide of the amino acid. Bergmann and his associates have shown that reactions with acylated diketopiperazines [10], histidine [11], theobromine [11], and other derivatives of substituted amides [12] in which an acyl group is attached to nitrogen, involve a rearrangement of this acyl group from its endo position to the amino acid, reacting with this compound. An alkaline reaction entails the formation of diacyl derivatives of a dipeptide [10], coming from the diacylated diketopiperazine.

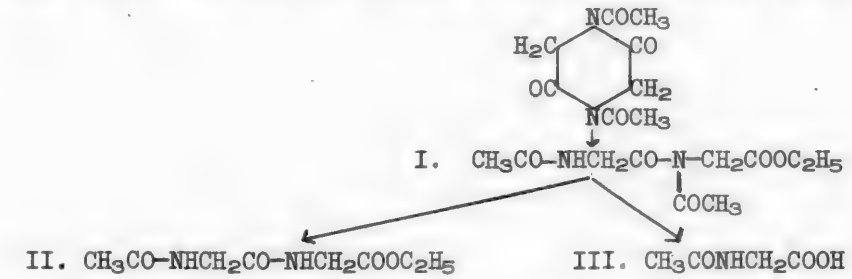


Diagram 5.

Bergmann also observed a decomposition of this sort when arginine acted upon diacetyldiketopiperazine in alcoholic solution. A singular property of such a twice acylated peptide is that it is saponified by an alkali to acetyl-glycyl-glycine, instead of being cleaved and yielding aceturic acid.

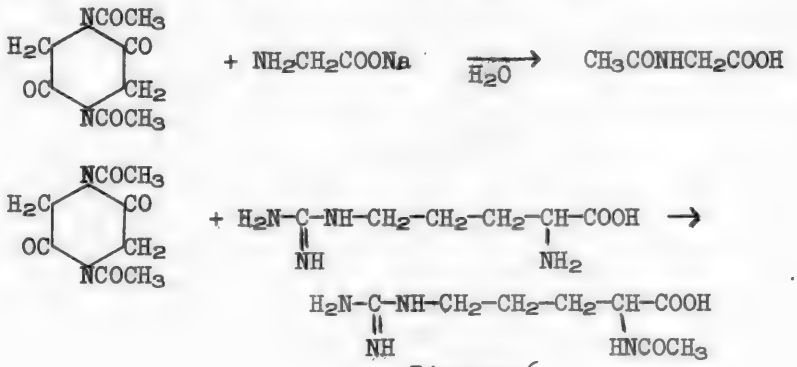


Diagram 6

Bergmann therefore held that acylated substituted amides can act as acylating agents of the amino group of amino acids, as indicated in Diagram 6, and that with this he had discovered a synthetic approach to the acylation processes that take place in the living organism.

It seemed to us that there was little ground for accepting a reacylation process without a mechanism for the formation of intermediate compounds. Bergmann's researches enabled one to get an idea of the chemical actions involved in these transformations. In a series of researches extending from 1924 to 1927, Brunner [13] demonstrated a method of synthesizing amides from diacyl amides (Diagram 7), with the process noticed by Bergmann in the acylated ketoheteroamide rings occuring as a side reaction.

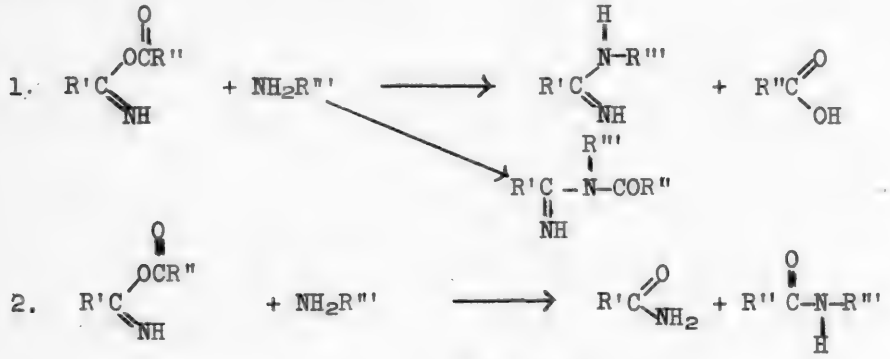


Diagram 7.

Only the process involved in the acylation of histidine does not fit into this scheme, for this involves an already acylated amidine. Our present paper also sheds light on this process of rearranging the acyl group from an acylated amidine to an acylated amine. In the simplest case of diacetyl-diketopiperazine and the sodium salt of glycine, the process must be pictured as follows: the carbonyl groups of the diacetyl-diketopiperazine become as reactive as the carbonyl groups of aldehydes and ketones, which leads to the addition of the amine and the formation of a compound of the Schiff base type. This is followed by a rearrangement of the acetyl group that is characteristic of acetylated amidines, and, lastly, by a breakdown of the resulting compound, with aceturic acid split off (Diagram 8). This diagram has been fully borne out in a series of experiments that we performed in order to check it. The reaction of diacetyl-diketopiperazine with a glycine ester may follow three different paths, depending upon the medium chosen. When the reaction with esters of the glycine as a base was carried out in alcohol, whether ethyl alcohol or methanol, compounds with the following general formula:

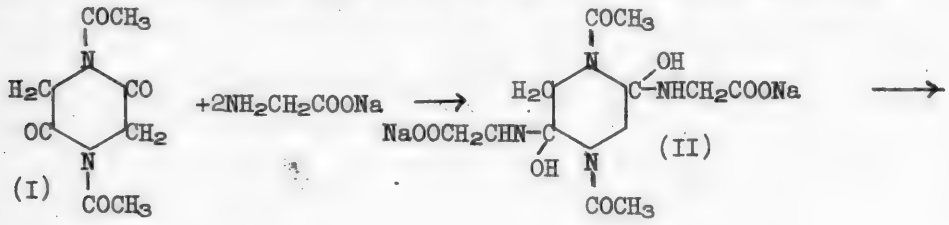


Diagram 8

were produced.

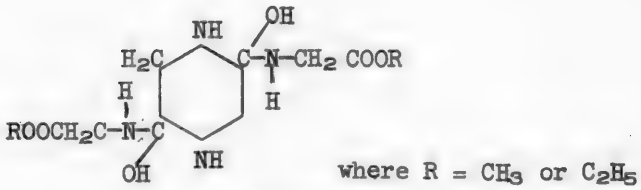


Diagram 9

When the reaction is performed in absolute alcohol, the foregoing compounds are not produced as a rule. A high yield of di-exo-N-acetyl-glycine-2,5-dihydropyrazin amidine (VII) is secured.

The data set forth above enable us to advance the following possible mechanism of the reaction (Diagram 10; R = C_2H_5). The initially formed di-endo-N-acetyl-glycine-ethyl ester of 2,5-dihydropiperazineamidine hydrate (V) is rearranged into the

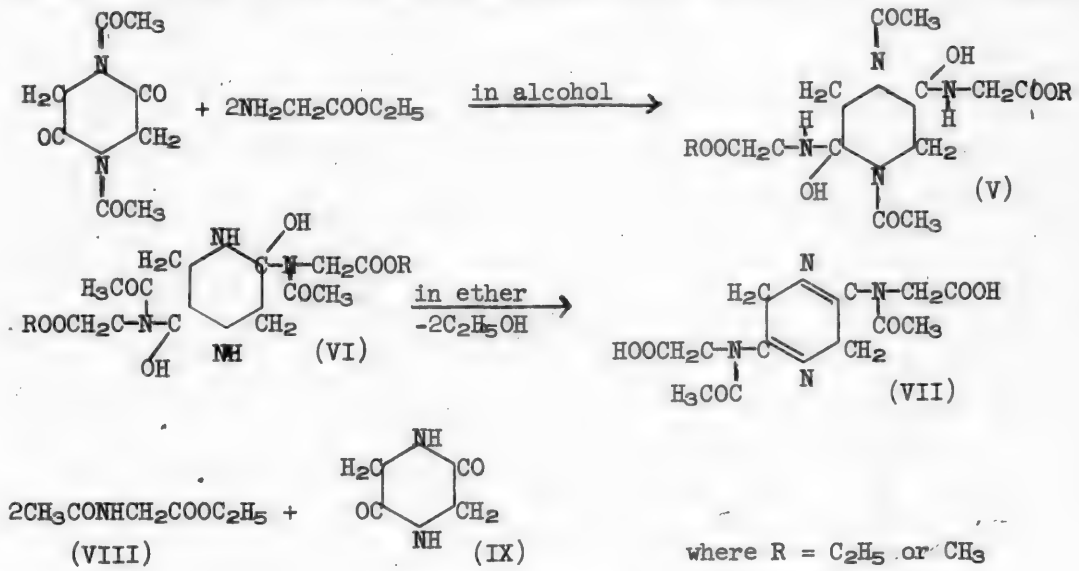


Diagram 10.

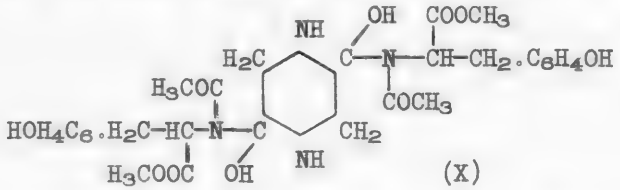
di-exo-N-acetylglycine ethyl ester of 2,5-dihydropyrazinamidine hydrate (VI). The latter either splits up into aceturic ester (VIII) and diketopiperazine (IX) or gives up a molecule of alcohol and is converted into di-exo-N acetyl-glycine-2,5-dihydropyrazinamidine (VII). Proof of the rearrangement of the acetyl group is in the breakdown of compound (VI) into diketopiperazine and aceturic ester. The latter was found in all the reactions in which diketopiperazine was recovered, as well as in our efforts to recrystallize the acetyl derivative of the amidine ester from alcohol.

Experiments have confirmed the scheme we have advanced and have enabled us to set down a number of rules concerning the feasibility of a link between amino acyls and the nitrogen of diketopiperazines.

Strange as it may seem, the compounds recovered by us from the reactions were not found by Bergmann. The only possible reason for this is his having focused his attention upon the nitrogen-acyl bond, which was considered to be an established fact in the era of E. Fischer, applying to all bonds between amino acids. Nature proved to be more bounteous, providing a mobile, multiform, and almost alive amidine bond instead of the half-dead peptide and rigid diketopiperazine bonds; we have established this bond for the first time, both by synthesis of models and by analysis of the protein molecule.

When diacetyl-diketopiperazine is reacted with glycine ester, the initial addition of the amino group to the carbonyl takes place nearly instantaneously. Diacetyl-diketopiperazine dissolves completely in alcohol within a few minutes, with the evolution of a slight amount of heat. What is not wholly understandable is the splitting off of ethyl alcohol from the ester group of the amino-acid constituent. Nevertheless, this splitting off was confirmed in the condensation of diacetyl-diketopiperazine with methyl glycine (Diagram 10: R = CH_3). In this reaction, which is quite similar to the one just described, we identified the methyl esters (VI) and (VIII), respectively, as well as the acetylamidine (VII), which was fully demonstrated by the first reaction (with the ethyl ester) and by the second (with the methyl ester). When condensation was effected in absolute ether with methyl- as well as with ethyl glycine, the only reaction product secured was di-exo-N-acetyl-glycine-2,5-dihydropyrazinamidine, and not its ester.

Though the condensation of diacetyl-diketopiperazine with tyrosine ester proceeds like that with the glycine esters in its first and second stages, the resulting di-exo-N-acetyl-tyrosine-methyl ester of 2,5-dihydropyrazineamidine hydrate (X) splits off alcohol neither in alcohol nor in ether. Though this compound is more stable than the corresponding derivatives of glycine, the detecting of a small amount of diketopiperazine and of acetyltyrosine ester forces us to consider the decomposition of acetylamidine esters to Bergmann's end formula, i.e., to diketopiperazine and acetylamino acids, as applying to all such esters. Since the di-exo-N-acetyl-tyrosine methyl ester of 2,5-dihydropyrazinamidine hydrate is identical with the acetate of the usual ester of tyrosinamidine,



(X)

we tried to convert this compound into the hydrochloride, which we already knew. The experiment showed us that what we were dealing with was still a hydrate of

acetylamidine, for the action of HCl in alcohol did not yield an amidine hydrochloride, the hydrochloride of the dipeptide glycyl-tyrosine ester being recovered with a nearly quantitative yield. Thus, the diketopiperazine ring was ruptured in this case. We observed a similar phenomenon in an endeavor to esterify di-exo-N-acetyl-glycine-2,5-dihydropyrazinamidine. Here again, we found that in a hydrochloric acid solution of ethyl alcohol ethyl acetate was formed, with a quantitative decomposition of the acetylamidine to a hydrochloride of the dipeptide ester. When diacetyl-diketopiperazine is condensed with amines, whether benzylamine or propylamine, the respective acetylamidines are formed, Here, as in most cases, the acetyl is shifted from the endo to the exo position. Some of the di-exo-N-acetylbenzyl-2,5-dihydro-pyrazinamidine breaks down, forming diketopiperazine and acetylbenzylamine. The acetyl group in 1,4-endo-N-acetyl-2-propyl-5-ketopiperazinamidine evidently remains in the endo position to the nitrogen, since no acetylpropylamine was found in the reaction products. Acetyldiketopiperazine dissolves in a solution of ammonia in ether, which indicates that a reaction occurs, but when the excess ammonia and ether are driven off in vacuum, all that remains behind is the acetylated diketopipera-zine (Diagram 11). No rearrangement of the acetyl group takes place, since we did not find any acetamide or diketopiperazine in the reaction products.

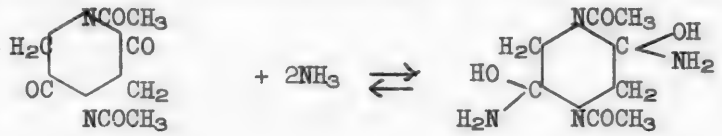
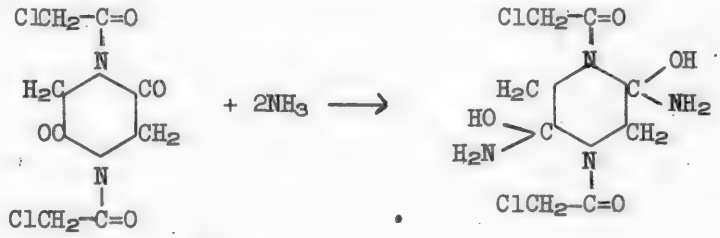


Diagram 11.

In an attempt to synthesize N-acylamine-diketopiperazines by the Abderhalden method, we have shown, together with Kh.N.Lerman, that: 1) the chlorine in di-chloroacetyl-diketopiperazine is not reactive; and 2) ammonia amonifies the acyl chloride group at the carboxyl, forming an amide, which is then aminated at the chlorine.

In the light of our present researches on diacetyl-diketopiperazine and of Bergmann's researches, the mechanism of this reaction must differ from that of analogous reactions taking place between diacetyl-diketopiperazine and an ester of an amino acid. We have confirmed this in our present research by reacting N,N'-di-chloroacetyl-diketopiperazine with esters of glycine and tyrosine. The former yielded the di-exo-N-chloroacetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate, as well as chloroaceturic ester. The ester group did not split off from the above-mentioned amine when the reaction was performed in (anhydrous) alcohol or ether. In the reaction with tyrosine ester we found the di-exo-N-chloroacetyl-tyrosine-methyl ester of 2,5-dihydropyrazinamidine hydrate in the reaction pro-ducts.



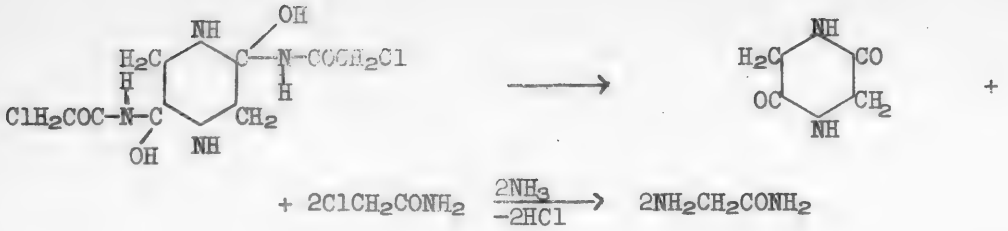


Diagram 12.

In contrast to unacylated or free amidines, the exo-acylated amidines we have investigated form fairly stable copper coordination compounds of the tripeptide type with a maximum at the wavelength of 660 mμ, (exo-acetyltyrosine ester of the amidine, with 1 atom of copper per molecule of the substance (1:1). The di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate is unstable in alkalies, being converted into N-acetyl-glycyl-glycine ester (Diagram 13). A copper coordination compound with a 1:2 copper-amidine ratio is formed after the former is allowed to stand for an hour with an alkali. Twelve hours later, this ratio rises to 1:2.9. If exo-acetylamidine broke down into an acetyldipeptide completely, the copper-substance ratio ought to have risen to 1:6.6. Hence, the decomposition of exo-acylated amines in acid and alcoholic or alkaline media results in the formation of dipeptide esters and acylated peptides, respectively, the latter involving the rupture of the piperazine ring. This phenomenon is confirmed by Bergmann's experiments, though he did not give a satisfactory explanation for the formation of these peptides.

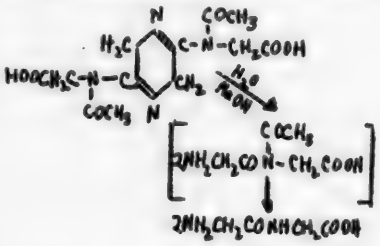


Diagram 13

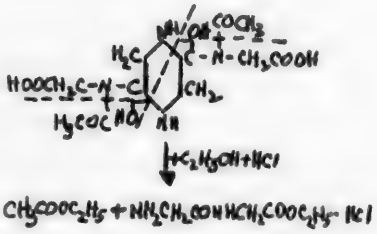


Diagram 14.

EXPERIMENTAL

Condensation of Diacetyl-diketopiperazine with Glycine Ester

We prepared diacetyl-diketopiperazine by acetylating diketopiperazine by boiling it for 5-6 hours with five times its weight of acetic anhydride dissolved in acetic acid. The diacetyl-diketopiperazine was recrystallized from alcohol after the solvent had been driven off in vacuum. M.p. 102°.

Condensation in absolute ethyl alcohol. 2 g of diacetyl-diketopiperazine was dissolved by heating it in 40 ml of absolute alcohol. The solution was cooled quickly, and 2.1 g (2 mols) of ethylglycine (n_D 1.4238), was added. The diacetyl-diketopiperazine dissolved quickly when the mixture was shaken up, and then a flocculent precipitate began to settle out. The precipitate was filtered out after the mixture had been allowed to stand for two hours, and then the filtrate and the precipitate were analyzed separately.

The precipitate was treated with absolute ethyl alcohol. Part of the precipitate did not dissolve; its properties (m.p. 316°; total nitrogen = 24.35% found, 24.56 computed) indicated that it was diketopiperazine.

The alcoholic filtrate was concentrated to small volume in vacuum, after which it was precipitated with absolute ether, and the precipitate was filtered out and washed. The substance was dried in a vacuum exsiccator; it then fused at 133.5-135°, was readily soluble in water, displayed an anhydride reaction (in the cold) and a biuret reaction of the dipeptide type (VI; R = C_2H_5; Diagram 10).

A Sørensen test indicated no amino nitrogen was present.

Found %: C 47.52, 47.60; H 7.09, 7.02; N 14.08, 13.93; M 389, 393 (Rast).
$C_{16}H_{28}N_4O_8$. Computed %: C 47.52; H 6.93; N 13.86; M 404.

The alcohol in the filtrate was driven off in vacuum. The residue had a basic odor and a strongly alkaline reaction. When absolute ether was added to it, a precipitate was formed; this was filtered out and washed with petroleum ether. The substance was dried in a vacuum exsiccator, after which it melted at 48°, which is the melting point of aceturic ester. Anhydrous hydrogen chloride was passed through the ether-petroleum ether filtrate; the resulting precipitate was identified as the hydrochloride of glycine ester (m.p. 145°, crystalline form).

Thus, although an acetylated amidine was produced, much of it decomposed, and the reaction resulted in our securing the di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate as well as diketopiperazine and aceturic ester.

Desiring to retard this decomposition, which might be due to the alkaline reaction produced by the free glycine ester, we repeated the experiment, adding an equimolar quantity of hydrochloric acid to the alcohol after the diacetyl-diketopiperazine had been dissolved. This yielded a small amount of the same hydrate of the exo-acetylated ester of the amidine and aceturic ester, plus diketopiperazine and glycine ester, both of which dropped out of the reaction.

Condensation in absolute methanol. 4 g of diacetyl-diketopiperazine was dissolved by heating with 80 ml of the absolute alcohol. After the solution had cooled 4.2 g of ethyl glycine was added. Special precautions were taken to obtain an absolute alcohol and an anhydrous glycine ester. After the diacetyl-diketopiperazine had dissolved and the whole had stood for half an hour, a small precipitate settled out; this was filtered out and treated with absolute ethyl alcohol. It proved to be diketopiperazine (20 mg). The two alcoholic solutions (methyl and ethyl) were evaporated in vacuum; after they had been reduced to small volume, precipitates were thrown down, consisting of mixtures of several substances. The precipitates were analyzed. The precipitate secured by treating the initial precitate with methanol was treated with acetone. The melting point and crystalline form of the part that did not dissolve indicated that it was diketopiperazine. The acetone solution was evaporated to small volume in vacuum without heating, and the resulting precipitate was filtered out, washed with ether, and dried in a vacuum exsiccator. M.p. 177-179°. It is readily soluble in acetone and in methanol, less so in ethyl alcohol. It displays an anhydride reaction (picric) in the cold and a biuret reaction of the dipeptide type. The ninhydrin reaction was negative (VII; Diagram 10).*

Found %: C 45.70, 45.93; H 5.30, 5.28; N 17.80 (Kjeldahl).
$C_{12}H_{16}O_6N_4$. Computed %: C 46.15; H 5.13; N 17.95.

The acid equivalent was determined by titration with 0.1 N NaOH against two indicators: neutral red and phenolphthalein. The percent equivalent found was 16.87. The computed equivalent, 17.08. We also treated the precipitate secured from the ethyl alcohol with acetone, evaporating the filtrate to small volume. The

*This compound may be monoacetyl-diketopiperazine, which has the same melting point and elementary composition.

precipitate that remained undissolved in the acetone proved to be diketopiperazine. The precipitate that settled out of the acetone filtrate was filtered out and washed with ether. Its melting point (134°), its nitrogen content, its reactions – positive picric and biuret, and negative ninhydrin — and its crystalline form indicated that it was the previously secured di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate. Crystals of diketopiperazine settled out of the alcoholic filtrates of both compounds when they were allowed to stand; these crystals were filtered out and identified. The filtrate left after the diketopiperazine had been filtered out was evaporated to small volume and precipitated with ether. The resulting crystals were filtered out, washed with ether, and dried in a vacuum exsiccator. The substance's melting point (134°), solubility, and basic reactions indicated that it was the di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate (VI). The alcohol-ether filtrate was concentrated to dryness in vacuum, dissolved in a small quantity of ether, and precipitated with petroleum ether. It was washed on the filter with the same petroleum ether and dried in a vacuum exsiccator, M.p. 48°.

Found %: N 9.63 (Kjeldahl). $C_8H_{11}O_3N$. Computed %: N 9.65. The substance is aceturic ester.

These experiments, namely, the recovery of the di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazineamidine hydrate, and the presence of diketopiperazine and aceturic ester in the reaction products, fully bore out the mechanism we had advanced for Bergmann's acetylation of amino acids by diacetyl-diketopiperazine.

Condensation in absolute ether. 2 g of diacetyl-diketopiperazine was mixed with 60 ml of absolute ether and 2.2 g of ethylglycine. The mixture was shaken up for 2 hours in a mechanical agitator until the solution was no longer alkaline. The resulting precipitate was filtered out, washed with absolute ether, and dried in a vacuum exsiccator. Weight: 2 g. M.p. 180°. Homogeneous crystals under the microscope. Readily soluble in water and displays a strong anhydride reaction in the cold, a dipeptide type of biuret reaction, and a negative ninhydrin reaction.

Found %: N 17.93 (Kjeldahl). $C_{12}H_{16}O_6N_4$. Computed %: N 17.95.

When the ether filtrate was evaporated to small volume in vacuum, crystals with a m.p. of 102° settled out; they proved to be diacetyl-diketopiperazine. When gaseous hydrogen was passed through the ether solution, crystals of the hydrochloride of glycine ester settled out.

Thus, the condensation of diacetyl-diketopiperazine with ethylglycine in ether involved the conversion of the resulting di-exo-N-acetylglycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate into merely one condensation product: di-exo-N-acetylglycine-2,5-dihydropyrazinamidine, alcohol being evolved.* We performed a similar condensation with an ester, but this time with the methyl ester of the amino acid, to check the correctness of the suggested process by which the alcohol group is split off, involving the conversion of the ester of an acylated amidine into a dicarboxylic amidine.

Condensation of Diacetyl-diketopiperazine with Methylglycine

In absolute ether. 2 g of diacetyl-diketopiperazine was mixed with 60 ml of absolute ether and 1.8 g of methylglycine. Nearly all the diacetyl-diketopiperazine dissolved after a few minutes had elapsed. After the mixture had been allowed to stand for 20 minutes, a precipitate was thrown down; it was filtered out and washed with absolute ether. The precipitate was then treated with the acetone. The small

*Here, too, it is possible that the compound is a monoacetyl-diketopiperazine (according to its analysis and melting point

amount of substance that did not dissolve proved to be diketopiperazine. The acetone solution was evaporated to small volume in vacuum and then precipitated with absolute ether. The precipitate was filtered out and washed with absolute ether. M.p. 179°. A test sample, mixed with the acylated amidine prepared in the experiment with the ethyl ester of glycine, exhibited no depression.

Found %: N 17.94 (Kjeldahl). $C_{12}H_{16}O_6N_4$. Computed %: N 17.95.

The ether filtrate was concentrated in small volume in vacuum and then precipitated with petroleum ether. The precipitate was filtered out, washed with petroleum ether, and dried in a vacuum exsiccator. M.p. 58°. The melting point of methyl aceturate is 58.5° [14].

Found %: N 10.58. $C_5H_9O_3N$. Computed %: N 10.69.

The substance is therefore the methyl ester of aceturic acid. This experiment of ours confirmed that the hydrated forms of exo-diacetyl-diglycine esters of dihydropyrzinamidines readily tend to split off either an alcohol group, forming carboxyls, or the N-acetyl-amino acid components of the amidines.

In absolute methanol. 2 g of diacetyl-diketopiperazine, finely pulverized in a mortar, was mixed with 20 ml of absolute methanol and 1.8 g of methylglycine. The precipitate dissolved after 5 minutes of shaking. Adding 0.2 g of glycine methyl ester made the solution basic. A precipitate settled out after the solution had stood several hours. It was filtered out, washed with absolute methanol; it was identified* as diketopiperazine. Filtrate was concentrated to $^1/_2$ its volume without heat in vacuum, precipitated with absolute ether. The resulting precipitate was filtered out, washed with ether, dried in a vacuum exsiccator. M.p. 142°. Properties: readily soluble in water, alcohols, acetone. Positive anhydride reaction when heated, negative ninhydrin reaction, dipeptide biuret reaction. Thus, the substance is the di-exo-acetylglycinemethyl ester of 2,5-dihydropyrazinamidine hydrate (VI; R = CH_3; Diagram 10).

Found %: C 44.58; H 6.35; N 14.76 (Kjeldahl); M 358 (Rast).
$C_{14}H_{28}O_8N_4$. Computed %: C 44.68; H 6.38; N 14.89; M 376.

The methyl ester of aceturic acid was recovered from the filtrate by the method described above.

Endeavor to esterify di-exo-N-acetylglycine-2,5-dihydropyrazinamidine. We had hoped that the ester group formed during esterification would split off an acetyl group, thus giving us the usual hydrochloride of glycinamidine. Absolute ethyl alcohol was saturated with anhydrous hydrogen chloride until it contained 1.17 g of the latter per 100 ml (which corresponded to 2.0 mols of hydrochloric acid per the amount of the amidine taken). 10 ml of the resulting solution was heated with 0.5 g of the acylated amidine, using a reflux condenser. Much of the precipitate dissolved within 10 minutes, the odor of ethyl acetate being present. After the solution had cooled, the precipitate was filtered out, and washed with a small amount of ethyl alcohol. Microscopic examination revealed that it was the unchanged acylated amidine. The precipitate was retransferred to alcohol containing HCl; it dissolved completely after 30 minutes of esterification. The alcoholic solution was precipitated with absolute ether. The precipitate was filtered out, washed with ether, and dried in a vacuum exsiccator. M.p. 182° with decomposition. It displayed a dipeptide biuret reaction. The anhydride and ninhydrin reactions were positive. The Beilstein test (for halogen) was positive.

Found %: N 14.21 (Kjeldahl); NH_2 7.16 (Sorensen). $C_{16}H_{12}O_3N_2 \cdot HCl$.
Computed %: N 14.25; NH_2 7.12.

The substance recovered is the hydrochloride of the ethyl ester of glycyl-glycine [18].

We checked this by heating diacetyl-diketopiperazine and diketopiperazine under the

*Melting point, form of the crystals

same acidity conditions. After one hour of heating, the diketopiperazine displayed a weak biuret reaction and did not decompose into a dipeptide. Heating diacetyl-diketopiperazine in alcohol with hydrochloric acid converted it into diketopiperazine, while splitting off acetyl groups as ethyl acetate. We have thus observed the specific behavior of the acylated amidine in alcohol with HCl, which differs from the behavior of diacetyl-diketopiperazine and diketopiperazine under the same conditions.

Condensation of diacetyl-diketopiperazine with methyltyrosine in absolute ether. The methyltyrosine was prepared by the Fischer method [15]. 2 g of diacetyl-diketopiperazine was comminuted in a mortar with 3.94 g of methyltyrosine. The mixture was transferred to a bottle, into which 50 ml of absolute ether was poured. The reaction was carried out by shaking the bottle on a mechanical agitator for 5 days. At first the contents had a basic reaction, but they turned neutral on the fifth day. After the reaction was complete, the precipitate was filtered out, washed with absolute ether, and dried in a vacuum exsiccator. Then the precipitate was dissolved in acetone in the cold, the insoluble part of the precipitate being filtered out and washed with acetone. It proved to be diketopiperazine upon analysis. The solvent was removed from the acetone filtrate by driving it off in vacuum without the use of heat.* The residue was again dissolved in a small quantity of acetone and precipitated with absolute ether. The precipitate was filtered out, washed with absolute ether, and dried in a vacuum exsiccator. M.p. 168°. Properties: soluble with difficulty in water, but soluble in acetone (from which it crystallizes out in characteristic rhombohedrons), in methyl and ethyl acetates, and in alcohols. It displays positive anhydride, Millon s, and biuret reactions. The latter yields a blue color. The ninhydrin reaction is negative.

Found %: C 56.94, 56.69; H 5.91, 5.93; N 9.58 (Kjeldahl); M 583.7 (Rast). $C_{28}H_{36}O_{10}N_4$. Computed %: C 57.14; H 6.12; N 9.52; M 588.

It does not titrate in the Wilstatter test. Dissolving it in 0.1 N alkali results in saponification of the ester groups, the amidine being titrated back for its two carboxyl groups. The indicator used was neutral red.

Determination of the acid equivalent by titrating with 0.1 N NaOH against 2 indicators: neutral red and phenolphthalein: Equivalent measured: 5.0 mg. Equivalent computed: 4.8 mg.

The ether filtrate of the basic precipitate was concentrated to small volume in vacuum. The precipitate thrown down after petroleum ether was added was filtered out and washed with petroleum ether. The substance was dried in a vacuum exsiccator, after which it fused at 120°. The figure given in the literature [10] for the melting point of the methyl ester of acetyltyrosine is 120°. It crystallizes in rosettes of crystals from methanol. Positive Millon's reaction; negative anhydride and ninhydrin reactions.

Found %: N 5.87 (Kjeldahl). $C_{12}H_{15}O_2N$. Computed %: N 5.91.

The foregoing experiment was repeated, and the resultant precipitate was recrystallized from methyl acetate. Upon standing, diketopiperazine separated out from the filtrate as before, which indicates that the di-exo-N-acetyl-tyrosine-methyl ester of 2,5-dihydropyrazinamidine hydrate decomposes in the Bergmann manner. That is why the subsequent experiments and the treatment involved were performed in the shortest possible time, the same acylated amidine, with a m.p. of 168° being recovered from the principal reaction product. The Kjeldahl figure for the nitrogen content was 9.76% instead of the 9.52% called for by theory. The filtrate also yielded acetyltyrosine ester, with a m.p. of 120°.

Synthetic acetyltyrosine ester fuses at 120° [16].

*The dry residue was recrystallized from methyl acetate, the insoluble portion of the residue again proving to be diketopiperazine. The solvent was removed from the methyl acetate filtrate in vacuum without the use of heat

Endeavor to convert the di-exo-N-acetyl-tyrosine-methyl ester of 2,5-dihydropyrazineamidine hydrate into its hydrochloride. 0.5 g of the acylated tyrosinamidine was heated for half an hour with a solution of HCl in methanol, on the basis of 2 mols of HCl per mol of the amidine. The odor of methyl acetate arose from the mixture. The alcoholic solution was concentrated in vacuum three times, an equal volume of benzene being added each time to remove any water that might be present in the solution. Then the alcoholic solution was precipitated with petroleum ether. The oil that settled out soon crystallized. The precipitate was filtered out, washed with petroleum ether, and dried in a vacuum exsiccator. M.p. 242°. The figure given in the literature [17] for the melting point of glycyl-tyrosine hydrochloride is 242°; it was readily soluble in water, but insoluble in ethyl acetate. It exhibits a dipeptide biuret reaction. Its ninhydrin reaction is negative. It contains a halogen.

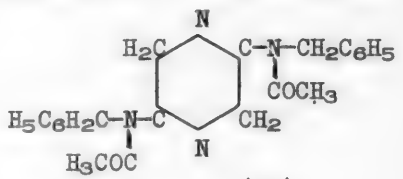
Found %: C 56.98; H 6.15; N 9.49 (Kjeldahl). $C_{13}H_{18}O_4N_2 \cdot HCl$.
Computed %: C 57.15; H 6.12; N 9.53.

Therefore, although the acetyl groups were split off when the di-exo-N-acetyl-tyrosinemethyl ester of 2,5-dihydropyrazineamidine hydrate is treated with alcoholic hydrochloric acid, the dihydropyrazine ring was ruptured at the same time, producing an ester of a glycyl-tyrosine dipeptide.

Condensation of diacetyl-diketopiperazine with benzylamine in absolute ether. 2.2 ml (2 mols) of benzylamine dissolved in 60 ml of absolute ether were added to 2 g of diacetyl-diketopiperazine in 60 ml of absolute ether. The solution solidified almost instantaneously when agitated; 30 more ml of absolute ether was added to it, and agitation was continued for 30 minutes. The resultant precipitate was filtered out and washed on the filter repeatedly with absolute ether.

The precipitate was dissolved in acetone in the cold. The undissolved portion proved to be diketopiperazine. The acetone filtrate was concentrated to small volume in vacuum. The resulting precipitate was filtered out and washed with a small quantity of ether. The precipitate was then recrystallized from methyl acetate, the insoluble portion of the precipitate again proving to be diketopiperazine. The methyl acetate filtrate and the acetone filtrate were separately concentrated to small volume in vacuum in the cold and then precipitated with absolute ether. The substances recovered from both solutions were dried in the vacuum exsiccator, after which they both fused at 148°. They were combined and recrystallized from acetone. M.p. 149°. Properties: the substance is soluble in methyl and ethyl acetates, acetone, and alcohols. It is insoluble in ether or petroleum ether. Its anhydride reaction is positive. The substance is di-exo-acetylbenzyl-2,5-dihydropyrazinamidine (XI).

Found %: C 70.36; H 6.17; N 14.76 (Kjeldahl); M 390 (Rast).
$C_{22}H_{24}O_2N_4$. Computed %: C 70.21; H 6.38; N 14.89; M 376.



(XI)

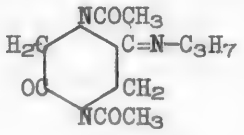
The first ether filtrate was concentrated to small volume in vacuum in the cold and then precipated with petroleum ether. The resulting precipitate was filtered out, washed with petroleum ether, and dried in a vacuum exsiccator. M.p. 60°. The figure given in the literature for the melting point of acetylbenzylamine is 60-61° [18]. It is soluble in all organic solvents, with the exception of petroleum ether. The ninhydrin, biuret, and anhydride reactions were negative.

Found %: N 9.28 (Kjeldahl). $C_9H_{11}O$. Computed %: N 9.39.

This substance is, therefore, acetylbenzylamine. The diketopiperazine and acetylbenzylamine recovered in this reaction indicate the general applicability of the reacylation mechanism we have suggested to amino acids as well as to amines.

Condensation of diacetyl-diketopiperazine with propylamine in absolute ether.

1.2 g of propylamine and 2 g of diacetyl-diketopiperazine (chilled with dry ice) were added to 100 ml of well-chilled absolute ether. Agitation for 5 minutes resulted in dissolution of the diacetyl-diketopiperazine, after which a copious precipitate began to settle out. The precipitate, filtered out and washed with ether, was dried in a vacuum exsiccator. M.p. 176°. Properties: readily soluble in methyl acetate, less so in acetone and methyl alcohol. It exhibits a strong anhydride reaction in the cold. Negative ninhydrin reaction. The substance is 1,4-endo-N-acetyl-2-propyl-5-ketopiperazinamidine (XII).



(XII)

Found %: C 74.38; H 7.18; N 17.56. (Kjeldahl). $(C_{11}H_{17}O_3)_2$. Computed %: C 74.50. H 7.11; N 17.57.

The ether filtrate turned cloudy after standing for a short time. The precipitate that settled out was filtered out and washed with absolute ether. There was very little of the precipitate, and under the microscope the crystals looked like neither diacetyl-diketopiperazine nor diketopiperazine, nor like the substance described above. No acetylpropylamine or diketopiperazine was recovered, which indicates that the acetyl group may be present in the endo position.

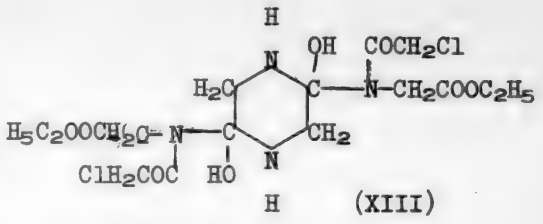
Condensation of diacetyl-diketopiperazine with ammonia in ether. We were unsuccessful in our effort to synthesize the simplest acetylated amidine of dihydropyrazine and ammonia. Although agitation of 0.5 g of diacetyl-diketopiperazine with ammonia dissolved in ether (2 mols of ammonia per mol of diacetyl-diketopiperazine) resulted in the former dissolving completely and the odor of ammonia disappearing, we were unable to secure an acetylated amidine by driving off the solvent. The precipitate recovered by concentrating the solution proved to be unchanged diacetyl-diketopiperazine. Evidently, the endo-diacetyl-dihydropyrazinamidine hydrate is reconverted into the original diacetyl-diketopiperazine by readily evolving ammonia in vacuum. The endo-acetyl group does not shift to the exo position, and we do not find any diketopiperazine or acetamide in the reaction products. This phenomenon is responsible for the negative result of our effort to prepare endo-N-diglycine-diketopiperazine.

Condensation of dichloroacetyl-diketopiperazine with ethylglycine.

In absolute ether. The dichloroacetyl-diketopiperazine, prepared by Abderhalden's method [20], was recrystallized from acetone. 2 g of N,N'-dichloroacetyl-diketopiperazine was mixed with 40 ml of absolute ether and 1.45 g (2 mols) of ethylglycine, and the whole shaken on a mechanical agitator for 20 minutes. The resulting precipitate was filtered out, washed with absolute ether, and dried in a vacuum exsiccator.

The precipitate was treated with acetone in the cold. Analysis of the part that did not dissolve showed it to be diketopiperazine (crystals under the microscope). The acetone filtrate was concentrated to small volume. The precipitate that settled was filtered out, washed with absolute ether, and dried in a vacuum exsiccator. M.p. 141°. It fused at 146° after recrystallization from ethyl acetate. Properties: a strong anhydride reaction in the cold, a negative ninhydrin reaction, and a dipeptide biuret reaction. It contains chlorine and is the di-exo-N-chloroacetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate (XIII).

Found %: C 40.67; H 5.40; N 12.00, 15.17 (Dumas method); Cl 16.18, 16.17 (Stepanov). $C_{16}H_{28}O_8N_4Cl_2$. Computed %: C 40.59; H 5.49; N 11.84, Cl 15.01.



(XIII)

The ether filtrate was chilled and concentrated to small volume in vacuum. The solution was precipitated with petroleum ether, and the precipitate filtered out. The precipitate was dissolved in ether and reprecipitated with petroleum ether. M.p. 63°. The figure given in the literature [21] for the m.p. of chloroaceturic ester is 62-63°.

Found %: N 7.95 (Kjeldahl). Computed %: N 7.80.

Hence, the substance recovered is chloroaceturic ester.

In absolute alcohol. We were unable to find the proper conditions for securing a chloroacetylated amidine in absolute alcohol. In twice-repeated experiments on the reaction of dichloracetyl-diketopiperazine with the glycine ester we secured nearly the theoretical yield of diketopiperazine in the precipitate and recovered a substance with a m.p. of 106° from the solution. The substance contained a halogen (Beilstein test), but it yielded no precipitate when treated with $AgNO_3$. It displayed a ninhydrin reaction and negative anhydride and biuret reactions. When this compound was dissolved in absolute alcohol and anhydrous HCl was passed through the solution for 5 minutes, after which a precipitate was thrown down with ether, a substance with a m.p. of 145° was recovered. It proved to be the hydrochloride of ethylglycine.

Analysis of the substance with m.p. of 106°: Found %: C 36.58, 36.62. H 6.00, 5.93; N 6.75 (Kjeldahl); Cl 6.47 (Stepanov). $C_8H_{12}O_4NCl$. Computed %: C 36.45; H 6.08; N 7.08; Cl 7.08.

Hence, the substance recovered is a salt of chloroacetic acid and ethylglycine.

Condensation of dichloroacetyl-diketopiperazine with methyltyrosine in absolute ether. 1 g of dichloroacetyl-diketopiperazine was comminuted in a mortar with 1.5 g of methyltyrosine. The mixture was transferred to a bottle containing 40 ml of absolute ether and agitated on a mechanical agitator for 10 hours. The precipitate was filtered out and analyzed separately from the ether filtrate.

The ether filtrate was concentrated to small volume in vacuum in the cold. The resulting precipitate was filtered out, washed with ether, and dried in a vacuum exsiccator above sulfuric acid. M.p. 136°. The substance recovered proved to be unreacted methyl tyrosine.

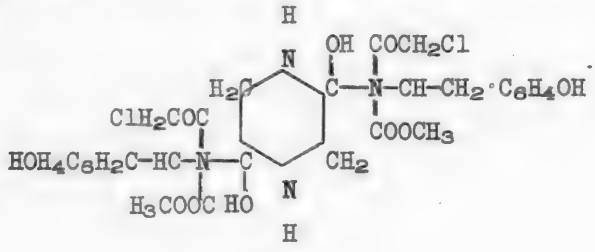
The precipitate was treated with $CHCl_3$ in the cold to eliminate the unreacted tyrosine ester. The chloroform solution was evaporated to small volume in vacuum and then precipitated with petroleum ether. The oil that settled out was treated with 1 N NaOH in the cold. Crystals of tyrosine settled out after the solution was neutralized with hydrochloric acid.

The precipitate that was insoluble in chloroform was treated with acetone. The insoluble portion proved to be diketopiperazine. When the acetone solution was evaporated in vacuum, the crystals that settled out contained diketopiperazine. They were redissolved in acetone without the use of heat, and the acetone solution was precipitated with absolute ether. The crystals were washed and dried, after which they fused at 160°. Properties: a strong anhydride reaction in the cold, a

positive biuret reaction, and a negative ninhydrin reaction. It contains a halogen.

Found %: C 51.22; H 4.96; N 8.47 (Kjeldahl); Cl 10.68 (Stepanov).
$C_{28}H_{34}O_{10}N_4Cl_2$. Computed %: C 51.14; H 5.17; N 8.52; Cl 10.8.

The substance is the di-exo-N-chloroacetyl-tyrosine-methyl ester of 2,5-dihydropyrazinamidine (XIV).



(XIV).

SUMMARY

I. We have succeeded in solving the chemism of the reactions of N,N'-acylated diketopiperazines with amino acids and some primary amines. In the reaction, the amino group of the second constituent is added to the carbonyl group of the acylated diketopiperazine, producing a hydrated form of the corresponding amidine, after which the acyl group is rearranged into the exo position. These exo-acylated amidines of the pyrazine series undergo two kinds of reactions: a) the acyl amine is split off, and the diketopiperazine regenerated; b) a molecule of alcohol is split off, forming di-exo-aminoacyl-2,5-dihydropyrazinamidines (?).

II. The following compounds have been secured and identified:

1. The di-exo-N-acetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate (VI).

2. The analogous methyl ester.

3. Di-exo-N-acetyl-glycine-2,5-dihydropyrazinamidine (VIII) (?).

4. The di-exo-N-acetyl-tyrosine-methyl ester of 2,5-dihydropyrazinamidine hydrate (X).

III. It has been shown that the action of a solution of HCl in alcohol or of an aqueous solution of alkali results in the nearly quantitative rupture of the ring, to esters of the respective dipeptides (glycyl-glycine, glycyl-tyrosine) in the former case, and to acetyl-N-glycyl-glycine in the latter.

IV. The following substances have been secured and identified:

1. Di-exo-N-acetyl-benzyl-2,5-dihydropyrazinamidine (XI).

2. 1,4-endo-N-acetyl-2-propyl-5-ketopiperazinamidine (XII).

V. The following substances have been recovered and identified from the condensation of dichloroacetyl-diketopiperazine with esters of glycine and tyrosine:

1. The di-exo-N-chloroacetyl-glycine-ethyl ester of 2,5-dihydropyrazinamidine hydrate (XIII).

2. The di-exo-N-chloroacetyl-tyrosine-methyl ester of 2,5-dihydropyrazinamidine hydrate (XIV).

VI. Exo-acylated amidines form copper coordination compounds of the tripeptide

type with a 1:1 copper-amidine ratio. Treatment of these amidines with alkali yields copper coordination compounds of the acetyl-dipeptide type.

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SPECTROPHOTOMETRY OF BIURET COORDINATION COMPOUNDS AS A METHOD OF INVESTIGATING PROTEINS

X. SPECTROPHOTOMETRIC INVESTIGATION OF BIURET-COPPER COORDINATION COMPOUNDS OF A HEPTAPEPTIDE AND AN OCTAPEPTIDE

M. I. Plekhan

As was shown in our last investigation of a heptapeptide biuret coordination compound [1], the spectrophotometric curve of this coordination compound greatly resembles the curves for tetra- and pentapeptides. As in these latter coordination compounds, the peptide-metal ratio is 1:1. We were interested in learning at what length of the polypeptide chain the second atom of copper is added to the coordination compound and what effect it has upon the spectrophotometric curve. With this in mind, we synthesized a heptapeptide (leucyl-pentaglycyl-glycine) and an octapeptide (leucyl-hexaglycyl-glycine). A spectrophotometric investigation has been made of the biuret coordination compounds of these peptides, covering the nature of their absorption, and the amount of metal in the coordination compound has been determined iodometrically. At the same time the position of the maxima has been defined more accurately in the spectrophotometric curves obtained earlier for the lower peptides. The results of the iodometric determination of Cu in the biuret coordination compounds of the hepta- and octapeptides have indicated that in these coordination compounds each peptide molecule has two copper atoms.

The spectrophotometric curves of the coordination compounds are shown in Fig. 1, with the values of the optical densities listed in Table 1. As the table indicates, the maximum for the heptapeptide coordination compound is located at a wavelength of 530 mμ, which points to the mixed nature of the coordination compound formed with this peptide. The shape of the curve as a whole shows that it belongs to the group of red coordination compounds. The structure of the heptapeptide coordination compound might be best represented as follows.

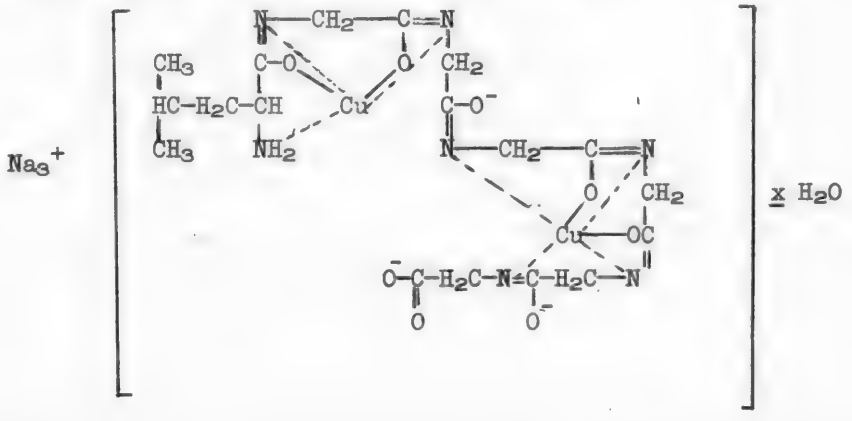


TABLE 1

Optical Density ε of Copper-Biuret Coordination Compounds of Glycyl Peptides. (Molar Concentration = 1:150)

Test No.	Wave length λ, mμ	Optical Density ε						
		Dipeptide (glycyl-glycine)	Tripeptide (diglycyl-glycine)	Tetrapeptide (triglycyl-glycine)	Pentapeptide (tetraglycyl-glycine)	Hexapeptide (alanyl-alanyl-triglycyl-glycine)	Heptapeptide (leucyl-penta-glycyl-glycine)	Octapeptide (leucyl-hexa glycyl-glycine)
1	480	0.054	0.222	0.599	0.792	0.734	0.978	1.044
2	490	0.066	0.252	–	0.901	0.844	1.136	–
3	505	0.078	0.310	0.786	1.020	0.942	1.332	1.340
4	510	–	–	–	1.030	0.962	–	–
5	515	–	–	–	1.030	0.964	–	–
6	520	0.93	0.360	0.830	1.020	0.964	1.434	1.360
7	523	–	–	–	–	–	–	1.360
8	525	–	–	–	–	–	–	1.360
9	530	0.108	0.392	0.820	0.991	0.932	1.436	1.336
10	535	–	–	–	–	–	1.434	1.302
11	540	0.118	0.416	0.760	0.905	0.876	1.426	1.266
12	550	0.132	0.442	0.678	0.861	0.792	1.358	1.200
13	560	0.149	0.451	0.597	0.738	0.710	1.268	1.120
14	570	0.167	0.460	0.511	0.628	0.628	1.170	1.026
15	575	–	0.463	–	–	–	–	–
16	580	–	0.457	–	–	–	–	–
17	582	0.192	0.443	0.420	0.510	0.544	1.022	0.934
18	600	0.228	0.423	0.299	0.367	0.392	0.824	0.784
19	610	0.251	0.393	0.252	0.312	0.334	0.736	0.694
20	620	0.278	0.374	0.218	0.259	0.284	0.630	0.604
21	630	0.301	0.351	0.188	0.211	0.212	0.600	0.526
22	640	0.322	0.330	0.174	0.177	0.178	0.550	0.450
23	650	0.352	0.313	0.162	0.149	0.148	0.506	0.374
24	670	0.395	0.280	0.139	0.104	0.096	0.448	0.250
25	693	0.385	0.240	0.123	0.068	0.064	0.406	0.150
26	710	0.349	0.191	0.112	0.051	0.044	0.352	0.102
27	730	0.271	0.134	0.093	0.036	0.028	0.272	0.066

In this coordination compound one atom of copper is linked as in a tetrapeptide coordination compound, the other's linkage being that of a tripeptide. Whether our hypothesis is correct may be tested by plotting a spectrophotometric curve for mixtures of the two tetra- and tripeptide coordination compounds, taken in equimolar quantities. We see that the mixture of coordination compounds of tetra- and tripeptides has an absorption that is quite similar to that of the heptapeptide coordination compound. The curves have a miximum at the same wave length. The slight difference in intensity may be due to the fact that the heptapeptide molecule contains a residue of the amino acid leucine, whereas the tetra- and tri-peptides contain nothing but glycine.

The biuret coordination compound of the octapeptide has an absorption maximum at the same wavelength as the tetrapeptide (520 mμ), though the intensity of absorption is much higher in the octapeptide coordination compound.

TABLE 2

Optical Density ε of Copper-Biuret Coordination Compounds of a Heptapeptide (1:300 Molar Concentration) and of a 1:1 Mixture of a Tetrapeptide and a Tripeptide (1:300 Molar Solutions)

Test No.	Wave-length, λ, mμ	Value of ε		Test No.	Wave-length, λ, mμ	Value of ε	
		Tetra- + tripeptide	Heptapeptide			Tetra- + tripeptide	Heptapeptide
1	480	0.431	0.489	12	600	0.362	0.412
2	490	0.493	0.568	13	610	0.325	0.368
3	505	0.575	0.666	14	620	0.292	0.325
4	520	0.623	0.717	15	630	0.260	0.300
5	530	0.628	0.718	16	640	0.250	0.275
6	535	0.624	0.717	17	650	0.228	0.253
7	540	0.620	0.713	18	670	0.208	0.224
8	550	0.583	0.679	19	693	0.184	0.203
9	560	0.550	0.634	20	710	0.157	0.176
10	570	0.505	0.585	21	730	0.123	0.136
11	582	0.448	0.511				

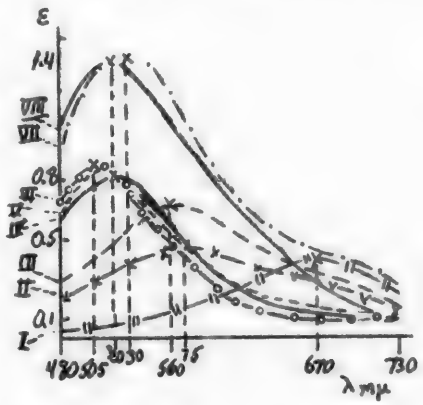


Fig. 1. Spectrophotometric curves of biuret-copper coordination compounds of polypeptides (1:150 molar solutions) and of casein (0.38% solution).

I-Dipeptide (glycyl-glycine); II-tripeptide (diglycyl-glycine); III-casein IV-tetrapeptide V-pentapeptide; VI-hexapeptide, VII-heptapeptide VIII-octapeptide.

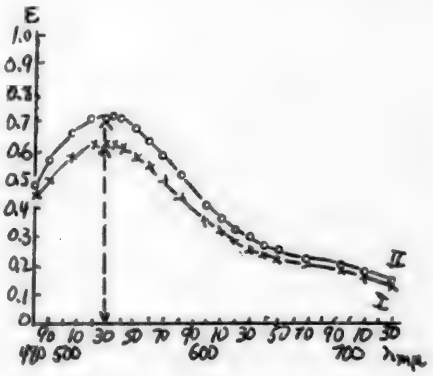
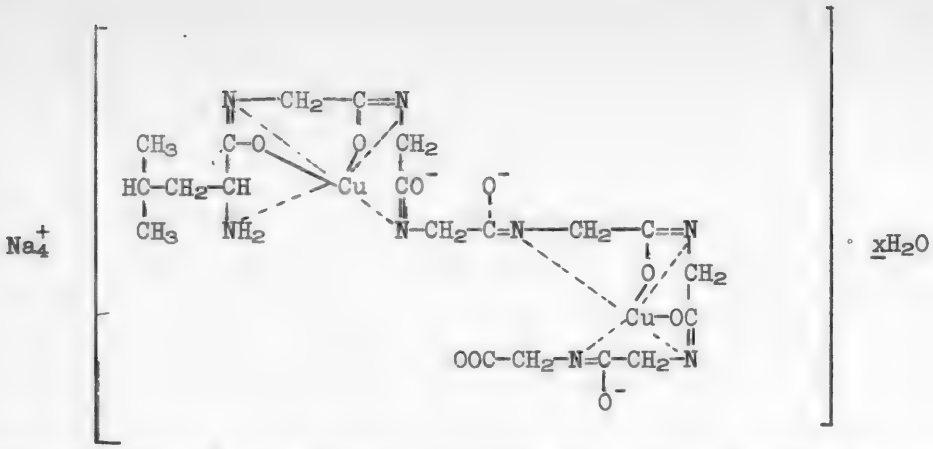


Fig. 2. Spectrophotometric curves of copper-biuret coordination compounds.

I-1:1 tetra- and tripeptide mixture (1:300 molar concentration); II - heptapeptide (leucyl-pentaglycyl-glycine) (1:300 molar concentration).

Inasmuch as the octapeptide coordination compound contains two copper atoms, we may suppose that it has the following structure: (See page 343).

Our results indicate that a tetrapeptide and polypeptides with a longer chain form copper-biuret coordination compounds belonging to the group of red coordination compounds, with an absorption maximum at the wavelengths of 515-530 mμ. The tripeptide forms a coordination compound with a maximum at a wavelength of 575 mμ. The



dipeptide coordination compound possesses an absorption maximum at a wavelength of 670 mμ.

As the chain is lengthened (after the tripeptide), the resemblance between the peptide coordination compound and a protein coordination compound disappears. For chains that are longer than an octapeptide, the formation of a coordination compound will probably involve the mazimum formation of red compounds, as the most complete ones, thus making a comparison with a protein coordination compound impossible.

EXPERIMENTAL

1. The hepta- and octapeptides were synthesized, in the main, by Fischer's methods [2]: condensing the acid chloride of Br-isocapronyl-diglycyl-glycine with a tripeptide in the first case and with a tetrapeptide in the second; the bromine was split off and replaced by an amino group by treatment with liquid ammonia for six days in a sealed tube at 25°. The resulting peptides were analyzed for the total and amino nitrogen. The percentages found for the heptapeptide leucyl-pentaglycyl-glycine, $C_{18}H_{31}O_8N_7 + 1H_2O$, were: total nitrogen 19.4; amino nitrogen 2.13. The computed percentages were: total nitrogen 19.9; amino nitrogen 2.85.

The corresponding percentages were as follows for the octapeptide leucyl-glycyl-glycine, $C_{20}H_{34}O_9N_8 + 1H_2O$; total nitrogen 20.98; amino nitrogen 2.07. The computed percentages were: total nitrogen 20.43; amino nitrogen 2.63.

The lower peptides were also synthesized by the Fischer methods.

2. The biuret coordination compounds of the heptapeptide and the octapeptide were prepared in the usual manner. The amount of heptapeptide used was 0.03849 g; the weight of octapeptide was 0.03534 g. The spectrophotometric curves of the di-, tri-, tetra-, and heptapeptide coordination compounds were plotted with the Kollemann electrospectrophotometer, Model 2. The curves for the penta-, hexa-, and octapeptides were made with a Beckmann instrument.

SUMMARY

1. The biuret coordination compound of the heptapeptide leucyl-pentaglycyl-glycine has an absorption maximum at a wavelength of 530 mμ. It contains 1 mol of the peptide and 2 mols of Cu. The coordination compound's curve resembles the curve for a 1:1 mixture of thecoordination compounds of tetra- and tripeptides.

2. The biuret coordination compound of the octapeptide leucyl-hexaglycyl-glycine has an absorption maximum at the wavelength of 520 mμ. It contains 1 mol of the peptide and 2 mols of Cu. The shape of the coordination compound's curve repeats that of the tetrapeptide curve, but the absorption intensity is much

higher in the octapeptide coordination compound.

3. The curves of the hepta- and octapeptide coordination compounds display no resemblance to that of the casein coordination compound.

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SPECTROPHOTOMETRY OF BIURET COORDINATION COMPOUNDS AS A METHOD OF INVESTIGATING PROTEINS

XI. SPECTROPHOTOMETRIC INVESTIGATION OF THE FORMATION OF A COPPER-BIURET COORDINATION COMPOUND IN THE PRESENCE OF A MIXTURE OF DI-, TRI-, AND TETRAPEPTIDES

M. I. Plekhan

In our previous papers we have pointed out the close resemblance between the absorption maxima of a biuret-copper coordination compound of a protein and a corresponding compound of a tripeptide. We also noticed, however, a certain difference in the position of the maximum on the curves that are typical of protein coordination compounds. The maximum is shifted 10-20 mμ toward the shorter wavelengths. It is located at 560 mμ for casein, at 565 mμ for gelatine, and at 555 mμ for serum albumin, whereas our latest researches show that it is located at 575 mμ for a tripeptide. Evidently, the formation of a coordination compound in the protein molecule is of a mixed nature, i.e., it takes place with a mixture of peptides, the bulk of them being tripeptides. But to decide what peptides the protein molecule contains, and in what proportions, we have to know how the formation of a coordination compound occurs in a mixture of peptides. No one has made a study of this problem hitherto, and the change in the spectroscopic curve as a whole is unknown.

Up to the present time our researches on biuret coordination compounds of peptides have dealt with individual substances; we secured the pure spectra characteristic of any one group of coordination compounds, i.e., red, violet, or blue. This research began with a study of the formation of a coordination compound in solutions containing several peptides with differing chain lengths. These investigations likewise enable us to shed light on some processes involved in the destruction of the protein molecule, in which we can always count on the formation of a mixture of peptides and amino acids.

1. The Formation of a Coordination Compound in a 1:1:1 Mixture of a Tetra-, Tri-, and Dipeptide

We were primarily interested in learning how a coordination compound is formed when a copper salt is gradually added to a mixture of three peptides of equal molar concentration (M:100) in an alkaline medium. Whenever the copper salt was added, the absorption of light by the resulting solution of a coordination compound was measured spectrophotometrically. We were thus able to follow the step-by-step changes in the curve. Our measurements are given in Table 1 and Fig. 1.

It must be remembered that the tetrapeptide is the first to react, forming a red coordination compound; 0.2 ml of the copper salt solution binds only the tetrapeptide

TABLE 1

Change in the Optical Density ε as Copper-Biuret Coordination Compounds are Gradually Formed in a 1:1:1 Mixture of Glycyl Tetra-, Tri-, and Dipeptides (M:100 Concentration)

Test No	Wavelength, λ, mμ	Value of ε with varying amounts of 0.25 M $Cu(CH_3COO)_2$						
		0.1 ml	0.2 ml	0.3 ml	0.4 ml	0.5 ml	1.0 ml	2 ml (excess)
1	480	0.223	0.572	0.820	0.90	0.975	1.01	1.048
2	490	0.311	0.664	0.930	1.04	1.04	1.175	1.215
3	505	0.338	0.750	1.080	1.21	1.21	1.390	1.470
4	510	0.342	–	–	–	–	–	–
5	515	0.345	0.760	1.125	1.30	1.46	–	–
6	520	0.33	0.765	1.125	1.315	1.48	1.540	1.665
7	525	0.329	–	1.11	1.315	1.510	–	–
8	530	0.317	0.750	1.09	1.31	1.510	1.60	1.74
9	540	0.292	0.662	1.025	1.275	1.49	1.63	1.785
10	550	0.251	0.597	0.925	1.18	1.43	1.65	1.80
11	560	0.217	0.503	0.810	1.075	1.35	1.68	1.762
12	570	0.183	0.423	0.695	0.96	1.22	1.61	1.755
13	582	0.144	0.335	0.552	0.82	1.06	1.60	1.687
14	600	0.103	0.230	0.397	0.628	0.87	1.55	1.600
15	610	0.087	0.192	0.333	0.540	0.765	1.52	1.56
16	620	0.070	0.162	0.278	0.473	0.67	1.47	1.51
17	630	0.066	0.141	0.245	0.416	0.592	1.45	1.47
18	640	0.057	0.130	0.218	0.378	0.541	1.42	1.432
19	650	0.052	0.115	0.200	0.339	0.491	1.37	1.38
20	670	0.048	0.107	0.174	0.293	0.411	1.29	1.335
21	693	0.047	0.101	0.153	0.249	0.337	1.20	1.177
22	710	0.047	0.091	0.128	0.199	0.276	0.91	0.997
23	730	0.045	0.077	0.100	0.149	0.163	0.71	0.702

into a coordination compound, as is indicated by the position of the maximum and the shape of the entire curve. The next to react is the tripeptide, the maximum beginning to shift toward the longer wavelengths. The absorption begins to increase in the wavelength region above 600 mμ. If the second constituent to enter into the reaction were the dipeptide, rather than the tripeptide, the absorption in this region would exhibit a second maximum. In our case the formation of a coordination compound comes to a close with the entrance of the dipeptide into the reaction, and the overall curve, the top curve in Fig. 1, actually possesses a second distinguishable maximum at 670 mμ. The first maximum is at 550 mμ. Thus, we can assert, on the basis of this experiment, that the red coordination compound is the first to be formed, as was to have been expected; hence, its activity and the ease of its formation are highest of the three. The second peptide to react is the tripeptide, followed by the dipeptide. Another point is that the resulting overall curve, which represents the light absorption by the mixture of all three coordination compounds, differs from the curves that are typical of protein coordination compounds. This difference is most apparent in the section of the curve that reflects the appearance of the dipeptide coordination compound.

2. Checking the Additivity of Absorption in the Formation of Coordination Compounds in a Mixture of Tetra-, Tri-, and Dipeptides

We were interested in the following question: does the mixture of three copper

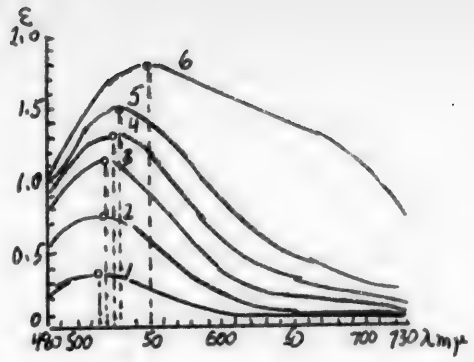


Fig. 1. Spectrophotometric curves of the experiment involving the formation of a biuret coordination compound when 0.25 molar $[Cu(CH_3COO)_2]$ is added to a 1:1:1 mixture of tetra-, tri-, and dipeptides (Peptide concentration = M:100.) 1-0.1ml; 2-0.2 ml; 3-0.3 ml; 4-0.4 ml; 5-0.5 ml; 6-2.0 ml (excess).

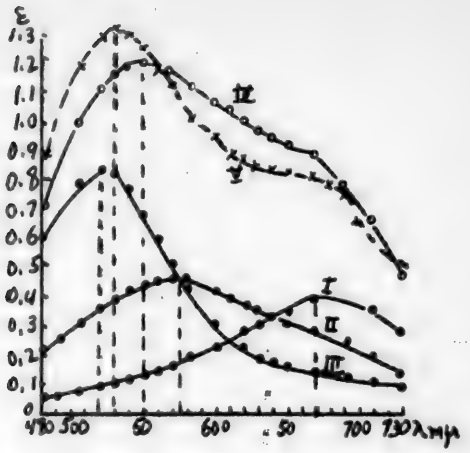


Fig. 2. Spectrophotometric curves of biuret coordination compounds of peptides (M:150 concentrations) and of their 1:1:1 mixture.

I-Dipeptide; II-tripeptide; III-tetrapeptide; IV-1:1:1 mixture of the peptides; V-arithmetical sum of ε.

coordination compounds of the tetra-, tri-, and dipeptides produced in the experiment described above possess additive properties with regard to the absorption of light? In other words, is the coordination compound of each peptide formed as if the latter were alone in solution, or does the presence of the other peptides affect the nature of the formation of the coordination compound in some way? We solved this problem as follows. We made separate spectrophotometric measurements of solutions of the copper-biuret coordination compounds for the tetra-, tri-, and dipeptides (at M:150 concentrations). Our results are shown in Table 2 and Fig. 2. The optical densities ε of all three coordination compounds were added arithmetically at each wavelength. This gave us the arithmetic sum of ε. These figures are tabulated in Table 2 and plotted in Fig. 2. The experimental sum of ε (as found in the experiment described above) is listed in Table 2 and plotted in Fig. 2 for the sake of comparison.

The arithmetical and experimental sums of ε do not coincide, as is seen in Fig. 2. Hence, the formation of a coordination compound changes for some one of the three peptides, which behaves differently in a mixture than in an individual solution.

3. Dislodgement of Peptides from Coordination Compounds by One Another

The experiment described at the beginning of the present paper showed us that the activity of formation of the red coordination compound is much higher than that of the violet or blue compound. This phenomenon was confirmed as follows:

The tripeptide was added to the blue solution of the dipeptide's copper-biuret coordination compound, which is represented by Curve I in Fig. 3. The solution turned violet almost instantaneously. The resulting solution is represented by Curve II.

TABLE 2

Optical Densities ε of M:150 Copper-Biuret Coordination Compounds of Individual and Mixed Peptide Solutions

Test No.	Wavelength, λ, mμ	Value of ε for a M:150 Solution				Arithmetical sum ε
		Dipeptide	Tripeptide	Tetrapeptide	Experimental sum	
1	480	0.054	0.222	0.599	0.699	0.875
2	490	0.066	0.252	–	0.810	–
3	505	0.078	0.310	0.786	0.980	1.174
4	520	0.093	0.360	0.830	1.110	1.283
5	530	0.108	0.392	0.820	1.16	1.32
6	540	0.118	0.416	0.760	1.19	1.294
7	550	0.132	0.442	0.678	1.20	1.252
8	560	0.149	0.451	0.597	1.175	1.197
9	570	0.167	0.460	0.511	1.17	1.138
10	575	–	0.463	–	–	–
11	580	–	0.457	–	–	–
12	582	0.192	0.443	0.420	1.125	1.055
13	600	0.228	0.423	0.299	1.07	0.951
14	610	0.251	0.393	0.252	1.04	0.896
15	620	0.278	0.374	0.218	1.01	0.870
16	630	0.301	0.351	0.188	0.98	0.840
17	640	0.322	0.330	0.174	0.955	0.826
18	650	0.352	0.313	0.162	0.925	0.829
19	670	0.395	0.280	0.139	0.890	0.814
20	693	0.385	0.240	0.123	0.785	0.748
21	710	0.349	0.191	0.112	0.665	0.682
22	730	0.271	0.134	0.093	0.468	0.498

in Fig. 3 and by the corresponding values of ε in Table 3. (It should be noted that Curve II differs somewhat from the curve for the tripeptide.) The tetrapeptide was added to the violet solution, turning the solution red instantaneously. This solution is represented by Curve III in Fig. 3 and by the corresponding values of ε in Table 3.

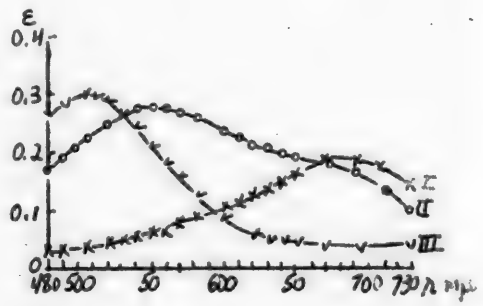


Fig. 3. Spectrophotometric curves of the experiment on the dislodging of a peptide from a copper-biuret coordination compound: tetrapeptide (III); tripeptide (II); dipeptide (I).

The changes in color that we observed in this experiment indicate that the tripeptide drives the dipeptide out of the coordination compound. The tetrapeptide, in turn, drives the tripeptide out and forms a red coordination compound when the tri- and dipeptides are also present. Thus, we always get the red coordination compound exhibiting maximum activity of formation, whether the copper salt is added to a mixture of all three peptides or the peptides are added step by step to the reaction. It is obvious that whenever a solution contains peptides

TABLE 3

Change in the Optical Densities ε Due to Peptides Dislodging One Another in a Copper Biuret Coordination Compound

Test No.	Wave-length, λ, mμ	Value of ε			Test No.	Wave-length, λ, mμ	Value of ε		
		I, dipep-tide	II-tri peptide added	III-tetra-peptide added			I, di-peptide	II - tri-peptide added	III - tetra-peptide added
1	480	0.032	0.174	0.266	12	600	0.108	0.243	0.092
2	490	0.034	0.196	0.288	13	610	0.118	0.230	0.084
3	505	0.041	0.225	0.302	14	620	0.128	0.219	0.064
4	510	–	–	0.305	15	630	0.140	0.214	0.061
5	520	0.045	0.248	0.294	16	640	0.153	0.203	0.053
6	530	0.054	0.264	0.274	17	650	0.163	0.196	0.050
7	540	0.058	0.277	0.243	18	670	0.191	0.185	0.047
8	550	0.067	0.279	0.215	19	693	0.191	0.171	0.039
9	560	0.070	0.277	0.187	20	710	0.176	0.140	0.05
10	570	0.082	0.275	0.159	21	730	0.147	0.108	0.047
11	582	0.092	0.266	0.131					

that can form a red coordination compound, they will be the first to react. Once, when elaborating a method for the titrometric determination of copper combined in a protein biuret coordination compound, we noticed that the first drop of the copper salt added to an alkaline solution of the protein always produced a pale pink coloring, after which the intense violet color began to be formed. Apparently, the appearance of this pink is due to the presence within the protein molecule of a small quantity of peptides that form red coordination compounds.

EXPERIMENTAL

1. Formation of Coordination Compounds of the Mixture of Tetra-, Tri-, and Dipeptides

The experiment was performed as follows: A 0.25 molar solution of $Cu(CH_3COO)_2$, K = 0.978, was added to a mixture of 2 ml of a 0.05 molar solution of a (glycyl) tetrapeptide, 2 ml of a 0.05 molar solution of a (glycyl) tripeptide, and 2 ml of a 0.05 molar solution of a (glycyl) dipeptide in such a manner that the first 0.5 ml was added 0.1 ml at a time, after which 0.5 ml was added all at once, and, lastly, 1 more ml of the copper salt and 4 ml of H_2O were added. This caused the excess copper hydroxide to be precipitated; it was filtered out 1 hour later. Spectrophotometric readings were taken after each addition of the copper salt. Thus, reading I corresponded to 0.1 ml of the copper salt; II to 0.2 ml; III to 0.3 ml; IV to 0.4 ml; V to 0.5 ml; VI to 1.0 ml; and VII to an excess (2 ml), i.e., the end of any formation of a coordination compound. Since the volume was changed by the time of Reading VII (15 ml instead of 10 ml), these figures were recomputed for a volume of 10 ml for ease of comparison; i.e., the concentrations of all the peptides were taken as M:100. These figures are listed in Table 1. The figures obtained experimentally for Reading VII are listed in Table 2 under the column heading

"Experimental sum"; they correspond to a concentration of M:150 for each peptide.

The spectrophotometric measurements were made with a Kollemann electric spectrophotometer, Model 2.

2. Checking the Additivity of Absorption in the Formation of Coordination Compounds of a Mixture of Tetra-, Tri-, and Dipeptides

Separate solutions of biuret coordination compounds of the peptides were prepared as follows: 2 ml of a 0.05 molar solution of the peptide, 10 ml of H_2O, 2 ml of 2 **N** NaOH, and 1 ml of 0.25 molar $Cu(CH_3COO)_2$ were mixed together.

The excess hydroxide was filtered out after 1 hour had elapsed, and spectrophotometric readings of the solution were made. The results are shown in Table 2 and Fig. 2. The arithmetical sum of ε was obtained by adding the optical densities at each wavelength at which readings were taken. At $\lambda = 480$ mμ, for instance:

0.054	+ 0.222	+ 0.599	= 0.875
ε dipeptide	ε tripeptide	ε tetrapeptide	arithmetical sum of ε for $\lambda = 480$ mμ.

3. Peptides Dislodging Each Other From a Coordination Compound

The experiment was performed as follows: 4 ml of a M:100 solution of the dipeptide, 1 ml of 2 **N** NaOH, 8 ml of H_2O, and 1 ml of 0.25 molar $Cu(CH_3COO)_2$ were mixed together. One hour later the excess copper hydroxide was filtered out of the solution and the spectrophotometric readings were taken (cf Curve I, Fig. 3, and Table 3).

4 ml of a M:100 solution of the tripeptide was added to 5 ml of the above-mentioned blue solution of the dipeptide biuret coordination compound, and the violet solution was analyzed spectrophotometrically 20 minutes later. Since this solution was more highly diluted with respect to copper than the initial solution of the dipeptide coordination compound, it was converted to a volume of 5 ml by multiplying all values by 9/5, in order to facilitate comparison of the ε readings. The results are listed in Table 3 and are represented by Curve II in Fig. 3.

5 ml of a M:100 solution of the tetrapeptide was added to the 9 ml of violet solution. Spectrophotometric readings were taken of the resulting red solution. The ε readings were converted to a basis of 5-ml volume by multiplying them by 14/5. The results are shown in Table 3 and in Curve III of Fig. 3. Thus, all the values of ε given in Table 3 refer to the same concentration of copper.

SUMMARY

1. When a tetra-, tri-, and dipeptide are all present in a solution of the same time, gradual addition of a copper salt causes a copper-biuret coordination compound to be formed as follows: first the tetrapeptide enters into reaction, causing the solution to turn red; then the tripeptide reacts, and lastly the dipeptide. The overall curve has its principal absorption maximum at a wavelength of 550 mμ and a second distinguishable maximum at the wavelength of 670 mμ. The shape of the overall curve differs greatly from that of a characteristic protein curve.

2. When present in solution together, tetra-, tri-, and dipeptides form a mixture of biuret copper coordination compounds whose light absorption is not the arithmetical sum of the absorption of the coordination compounds of these separate peptides.

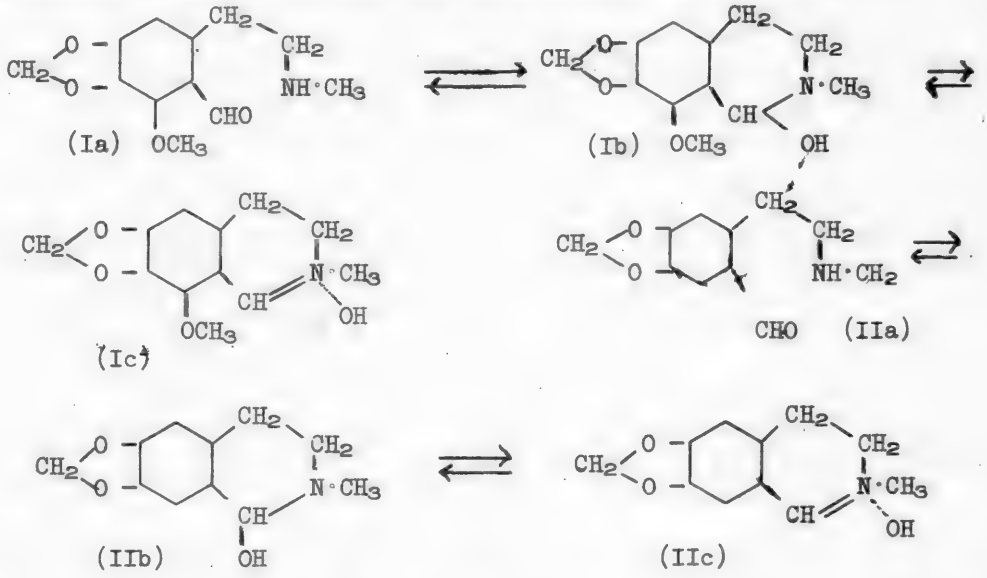
3. The red biuret coordination compound is formed so much more actively and readily than the violet or blue that the tetrapeptide dislodges the tripeptide and the dipeptide out of their coordination compounds when not enough copper is present for all three.

April 18, 1949. N.D.Zelinsky Laboratory of Protein Chemistry, University of Moscow

THE REACTIONS OF COTARNINE AND HYDRASTININE AND OF THEIR BENZOYL DERIVATIVES WITH CAUSTIC ALKALIES

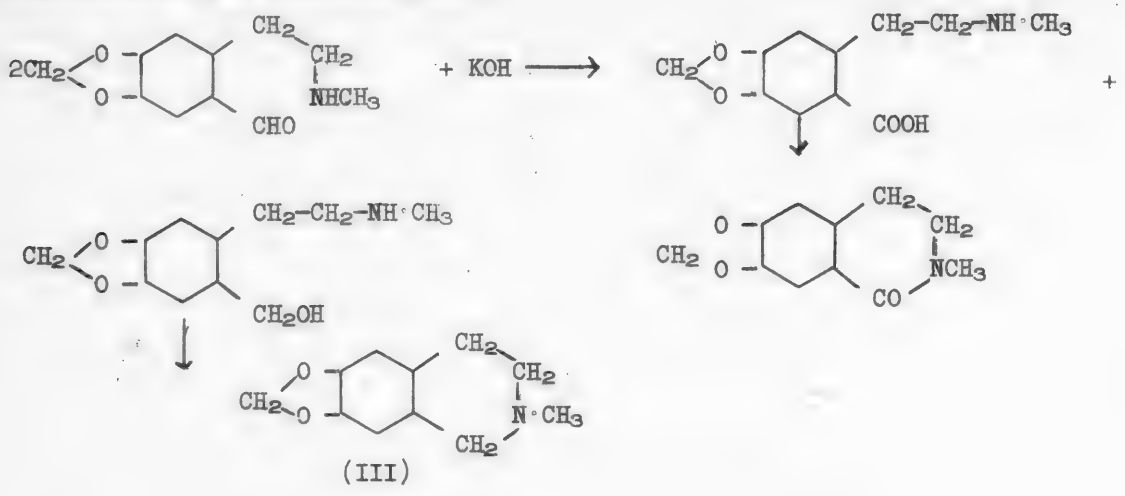
V. M. Rodionov and M. G. Chentsova

Cotarnine (I) and hydrastinine (II), the products of the oxidation of the alkaloids narcotine and hydrastine, respectively, are important pharmacologically because of their styptic qualities and have been the subject of more than one comprehensive investigation, it having been found that these compounds may react in various tautomeric forms, depending upon the prevailing conditions [1]:



The researches of Dobbie, Lauder and Tinkler [1], who made a study of the ultraviolet spectra of cotarnine and showed that in the solid state this compound has the (Ib) structure (put forward by Decker), though apparently possessing the (Ic) structure in solutions of dissociated solvents (the Roser formula, established for salts of cotarnine), are extremely interesting. Freund [2] considers the reaction of hydrastine with an alkali as a proof of the possible formation of its iminoaldehydic form (IIa). In this reaction the first stage is an oxidation-reduction process like the Cannizzaro reaction for the aldehydes, the resulting carbinol and acid losing a molecule of water and being converted into the bicyclic compounds

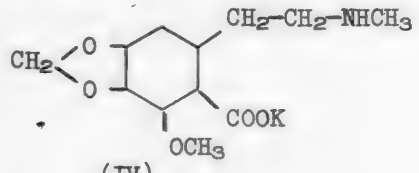
hydrohydrastinine and oxohydrastinine:



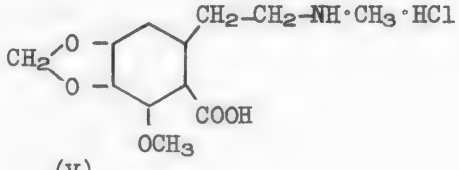
(III)

No such reaction is known for cotarnine, however.

This led us to make a study of the effect of alkalies upon cotarnine as well. Experiments have shown that the action of KOH upon cotarnine under the conditions described by Freund [2] for hydrastinine (boiling with a 33% KOH solution for 15 minutes) results in pronounced tarring; when gentler heating is employed, much of the cotarnine is recovered unchanged. Using alcohol as the solvent makes it possible to effect the reaction at 60-70°, but here, again, the reaction is incomplete. The method used to recover the products of the reaction of an alkali with cotarnine are somewhat different from the method proposed by Freund, inasmuch as the oxidation product of cotarnine, in contrast to hydrastinine, does not yield a closed isoquinoline form so readily, forming a salt of an amino acid (IV) under these conditions, which is readily soluble in water, but cannot be extracted with ether:



(IV)



(V)

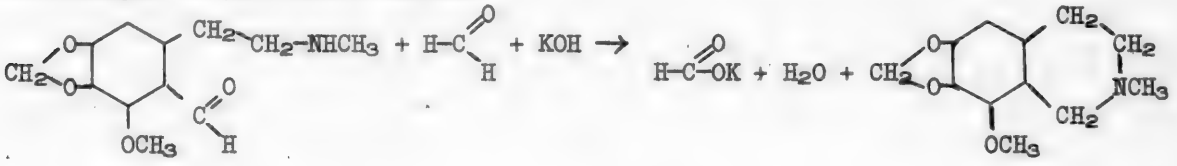
When the reaction mixture is acidulated with hydrochloric acid, no oxo compound is precipitated, but rather a hydrochloride of the amino acid (V), which is so stable that it can be recrystallized from water.

The corresponding product of the oxidation of hydrastinine – oxohydrastinine – has a closed isoquinoline form (III), and does not form stable salts when reacted with acids; it is therefore easily extracted with ether from acid aqueous solutions

We produced the closed form – oxocotarnine – by reacting silver oxide with an aqueous solution of the hydrochloride (V). The properties of the oxocotarnine prepared by our method are not entirely the same as those given by Freund and Wulff [2] for the compound they secured by oxidizing cotarnine with permanganate, which they called oxycotarnine. The Freund and Wulff product fuses at 108°, does not

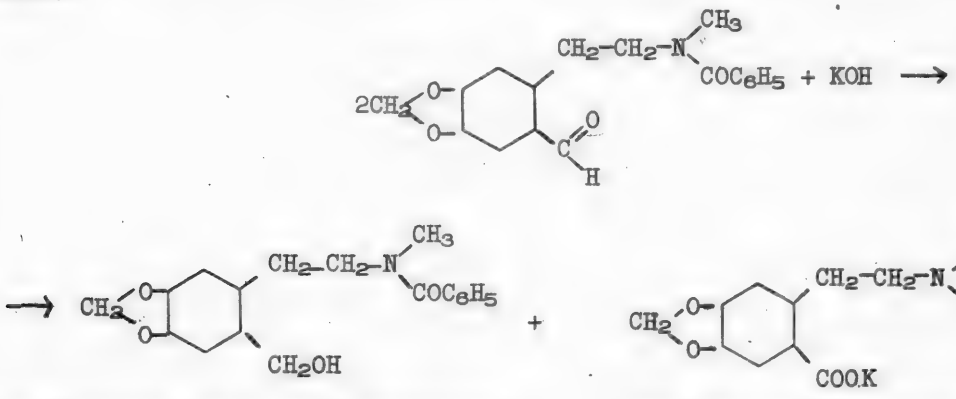
form stable salts with acids, and can be extracted with chloroform from acid solutions. Our substance, after having been dried over sulfuric acid, fuses at 147-149° with decomposition and (as has been mentioned above) dissolves in alkalies and forms water-resistant salts with acids.

The other reaction product – hydrocotarnine – was isolated by the method described by Freund for hydrohydrastinine. A high yield of hydrocotarnine is secured by using the so-called "cross reaction" suggested for the synthesis of aromatic alcohols [3], namely: reacting an alkali with a mixture of formaldehyde and an aromatic aldehyde in an alcohol medium.



In this reaction, the yield of hydrocotarnine, like that of hydrohydrastinine, is as high as 80%. It has thus been shown that cotarnine can react with an alkali in the same way as hydrastinine does, though under somewhat different conditions.

It is the benzoyl derivatives of these aldehydes that exhibit the greatest difference in their behavior toward an alkali. Whereas benzoyl hydrastinine reacts normally with an alkali, producing a high yield of the respective carbinol and acid:



2-β-(N-methyl-N-benzoyl)-aminoethyl-piperonyl alcohol

2-β-(N-methyl-N-benzoyl)-aminoethyl-piperonylic acid

benzoylcotarnine does not react with an alkali, either under ordinary conditions or in a cross reaction with formaldehyde. Like benzoyl cotarnine, another derivative of cotarnine – cotarnone – also does not react with an alkali. Apparently, the reactivity of cotarnine and its derivatives is lower than that of hydrastinine, owing to its containing a methoxy group and, especially, owing to the fact that this group is in the ortho position to the carbonyl group. As we know, the latter phenomenon is often enountered in the chemical literature [4].

EXPERIMENTAL

Action of an alkali upon cotarnine. 6 g of cotarnine – a base with a m.p. of 124°, 4 g of 50% KOH solution, and 5 g of ethyl alcohol were placed in a round-bottomed flask fitted with a stirrer and a reflux condenser. The mixture was heated to

80° (bath temperature) for 5 hours, with vigorous stirring, after which 50 ml of water was added and the whole was acidulated with hydrochloric acid. Elongated, yellow, acicular crystals of oxocotarnine hydrochloride soon settled out. They were filtered out, washed with water and alcohol, and dried in an exsiccator above sulfuric acid. The yield was 0.98 g, or 34% of the theoretical. The synthesized salt does not melt and decomposes above 300°. It is readily soluble in water, very highly soluble in alcohol, and slightly soluble in chloroform. It crystallizes from water

Found %: N 5.23, 5.17 (Dumas); Cl 13.09, 13.27 (Carius).
$C_{12}H_{14}O_4NCl$. Computed %: N 5.16, C 13.06.

The liquid remaining after the oxocotarnine hydrochloride had been filtered out was neutralized with NaOH until its reaction was sharply alkaline and then extracted with ethyl ether. The hydrocotarnine entered the ether layer, together with traces of the unreacted cotarnine. The hydrocotarnine was purified by reconverting it into the hydrochloride, neutralizing it with alkali, and extracting it with petroleum ether. After nearly all of the latter had been driven off, the hydrocotarnine crystallized out in colorless crystals containing $\frac{1}{2}H_2O$, with a m.p. of 49°. The yield was 0.45 g, or 19.31% of the theoretical. The melting point rose to 53-54° after recrystallization from dilute alcohol. A test sample, mixed with hydrocotarnine prepared by reducing cotarnine with Zn and H_2SO_4, exhibited no depression of the melting point. The melting point of the hydrochloride was 214-216°; that of the hydrobromide was 236°.

Recovering the base from oxocotarnine hydrochloride. 2 g of oxocotarnine hydrochloride (V) was dissolved in 60 ml of water; the solution was shaken up with an excess of freshly precipitated silver oxide and set aside to stand for 24 hours at room temperature. Then the precipitate was filtered out, and the filtrate was evaporated over a water bath to a volume of 8-10 ml and concentrated over sulfuric acid until a copious precipitate was thrown down. The filtered-out precipitate of oxocotarnine was desiccated above sulfuric acid; its m.p. was 147-149° with decomposition. The yield was 1.2 g, or 74% of the theoretical. Oxocotarnine is readily soluble in water, alcohol, and chloroform, much less so in benzene, and nearly insoluble in ether.

Found %: N 6.14 (Dumas). $C_{12}H_{13}O_4N$. Computed %: N 5.95.

Action of an alkali upon a formaldehyde-cotarnine mixture. 8 g of cotarnine (m.p. 124°), 8 g of ethyl alcohol, 17 g of a 30% formaldehyde solution, and 8 g of a 50% KOH solution were heated for 8 hours to 55-60° over a water bath with constant stirring. Nearly all the cotarnine precipitate dissolved. The liquid was cooled, filtered, diluted with water (40 ml), and extracted with ether. The aqueous layer contained a small quantity of tarry substances. The hydrocotarnine was extracted from the ether layer with dilute hydrochloric acid, and again extracted with petroleum ether after the acid solution had been alkalinized with NaOH. Driving off the ether yielded 6.4 g of air-dry hydrocotarnine as a transparent, slightly colored oil that crystallized upon standing. The yield was about 88% of the theoretical.

Action of an alkali upon a mixture of benzoylhydrastinine and formaldehyde. 1 g of benzoylhydrastinine (m.p. 98-99°), 10 ml of ethyl alcohol, and 3 g of a 35% formaldehyde solution were placed in a 50 ml flask, and 2 g of 50% KOH solution was added drop by drop. This caused the evolution of some heat, and most of the benzoylhydrastinine dissolved. The mixture was heated for another 3 hours over a water bath to 60° (bath temperature) with constant stirring, after which it was dissolved with water. Part of the resulting carbinol [2-β-(N-methyl-N-benzoyl)-aminoethylpiperonyl alcohol] was thrown down as a precipitate. Without filtering out the

precipitate, all the carbinol was extracted from the mixture by shaking the latter with benzene heated to 30°. Driving off part of the solvent caused the carbinol to separate out as lamellar white crystals with a m.p. of 110.5-112°, totaling 0.89 g. The substance is readily soluble in alcohol, benzene, ether, and acetic acid; only slightly soluble in water. The melting point was raised to 113° by recrystallization from alcohol or benzene. The yield was 88%.

Found %: N 4.73, 4.66 (Dumas). $C_{18}H_{18}O_4N$. Computed %: N 4.47.

The reaction also takes place at room temperature, though much more slowly. The formation of the carbinol was corroborated by converting it into a phenylurethane.

Synthesis of the phenylurethane of 2-β-(N-methyl-N-benzoyl)-aminoethylpiperonyl alcohol. A mixture, consisting of 0.8 g of phenyl isocyanate and 0.8 g of 2-β-(N-methyl-N-benzoyl)-aminoethylpiperonyl alcohol was heated to 160° over a sand bath for 1 hour. The resultant viscous mass was dissolved by heating it in benzene, and the mechanical impurities were filtered out. When it cooled, a white crystalline precipitate of the phenylurethane, totaling 0.8 g, or 77.3% of the theoretical, settled out. The melting point was 153° after recrystallization from alcohol.

Found %: N 6.74, 6.80 (Dumas). $C_{25}H_{24}O_5N_2$. Computed %: N 6.48.

Action of an alkali upon benzoylhydrastinine. A mixture consisting of 2 g of benzoylhydrastinine (m.p. 95-97°), 1 g of KOH, and 10 ml of ethyl alcohol, was heated to 40° over a water bath for 8 hours, after which it was diluted with water (20 ml) and extracted with benzene heated to 30°. The 2-β-(N-methyl-N-benzoyl)-aminoethylpiperonyl alcohol dissolved in the benzene; it was then recovered from the solution by driving off part of the solvent. Melting point 113° after crystallization from alcohol. The yield was 0.7 g, or 73%. The remaining alkaline liquid was acidulated with hydrochloric acid. The resulting 2-β-(N-methyl-N-benzoyl)-aminoethylpiperonylic acid was isolated as a viscous mass, which crystallized after several days had elapsed. It melted at 168° after recrystallization from dilute alcohol. The yield was 0.6 g, or 57% of the theoretical. Freund prepared this acid by oxidizing benzoylhydrastinine with permanganate and called it benzoyloxyhydrastinine hydrate. The compound we prepared is insoluble in soda, and reacts very slowly with an alkali; it is readily soluble in alcohol and acetic acid, and less so in ether or benzene; it is only slightly soluble in water. All these data agree with the properties of the compound synthesized by Freund.

Action of an alkali upon a hydrastinine-formaldehyde mixture. 2.5 g of a 50% KOH solution was added drop by drop to a mixture consisting of 3 g of hydrastinine hydrochloride (m.p. 207-210°), 6 g of a 35% formaldehyde solution, and 4 g of ethyl alcohol. The mixture warmed up by itself to 40°. After all the alkali had been added, heating was continued over a water bath to 65° for another 5 hours with constant stirring; then the mixture was diluted with water, and the hydrohydrastinine was extracted with ether. The ether was driven off, and concentrated hydrochloric acid was added to the residue; this turned the entire mass into a thick paste of white crystals of hydrohydrastinine hydrochloride. The yield was 1.95 g, or 70% of the theoretical. The melting point was 263° after double recrystallization from alcohol. The fact that the yield of hydrohydrastinine is lower that that of hydrocotarnine is due to the fact that the hydrastinine hydrochloride used for the reaction was not pure enough.

SUMMARY

1. A study of the reactions of potassium hydroxide with hydrastinine and cotarnine has shown that hydrastinine enters readily into a Cannizzaro reaction,

forming oxohydrastinine and hydrohydrastinine; under the same conditions (in aqueous solution) cotarnine is merely resinified.

2. When cotarnine is reacted with potassium hydroxide in an alcoholic solution, it enters into a Cannizzaro reaction, forming hydrocotarnine and the salt of the corresponding amino acid (IV).

3. Endeavors to effect a Cannizzaro "cross reaction" with formaldehyde demonstrated that cotarnine and hydrastinine both yield the corresponding hydro compounds.

4. The Cannizzaro reactions with benzoyl derivatives of hydrastinine and cotarnine, i.e., with compounds of an open-chain aldehyde form, are quite different. Benzoylhydrastinine reacts with an alkali readily, forming a carbinol and an acid. The benzoyl derivative of cotarnine does not enter into reaction under any conditions, being recovered unchanged from the reaction mass.

5. The following new compounds, not previously described in the literature, have been prepared: N-methylaminoethyl-methylenedioxy-methoxybenzenecarboxylic acid (IV) and its hydrochloride; N-methyl-N-benzoyl-aminoethylpiperonyl alcohol and its phenylurethane derivative.

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4-ALKOXY-PHENOXYACETIC ACIDS AND THEIR SIMPLEST DERIVATIVES

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Of the 4-alkoxy-phenoxyacetic acids, the only one described in the literature at the present time is 4-methoxyphenoxyacetic acid, which is prepared with a satisfactory yield by reacting sodium chloroacetate with hydroquinone monomethyl ether in an aqueous alkali solution [1]. These compounds are of some interest, however, even if only with respect to their activity toward acid-resisting microorganisms, since their having an ether group ought to facilitate their penetrating the waxy lipoid sheaths of microorganisms [2].

The 4-alkoxy-phenoxyacetic acids have been synthesized by reacting sodium chloroacetate with the phenolates of hydroquinone monoalkyl ethers in aqueous solution. The amides of these acids were prepared from chloroacetamide and the phenolates in alcohol. The 4-alkoxy-phenoxy-α-butyric acids were prepared from their phenolates and ethyl bromobutyrate, followed by saponification of the impure ester. The yields of all the compounds prepared were quite satisfactory.

EXPERIMENTAL

1. 4-Methoxyphenoxyacetic acid. Synthesized with a 51% yield. M.p. 112°.

4-Methoxyphenoxyacetamide, which is not described in the literature, was prepared as follows: 0.92 g of metallic sodium was dissolved in 40 ml of absolute ethyl alcohol, and 4.96 g of hydroquinone monomethyl ether and 3.74 g of chloroacetamide were added. The resulting mixture was boiled for an hour in a flask fitted with a reflux condenser. When the reaction was over, 100 ml of water was added to the mixture, and the precipitate was filtered out and washed with water. The amide was purified by recrystallizing it from water. The yield was 5.2 g (71.8%). A white crystalline substance with a m.p. of 116°.

0.1216 g substance: 12.45 ml 0.05 N H_2SO_4 used to bind the NH_3. 0.1415 g substance: 15.40 ml 0.05 N H_2SO_4 used to bind the NH_3. Found %: N 7.51, 7.62. $C_9H_{10}O_4N$. Computed %: N 7.73.

2. 4-Ethoxyphenoxyacetic acid. 16 g of hydroquinone monoethyl ether was dissolved in 100 g of 10% sodium hydroxide, and 11.3 g of monochloroacetic acid in 20 ml of water was added to the solution. The resultant mixture was heated for an hour over a boiling water bath. After it had cooled, the solution was acidified with hydrochloric acid and extracted with ether. The ether extract was washed with water and treated with a saturated soda solution. This caused the partial separation of sodium p-ethoxyphenoxyacetate, which is only slightly soluble in a soda solution. The ether layer was separated and the solution, together with its deposit, was treated with HCl. The resulting acid was crystallized from hot water. The yield

was 19 g (88%). White crystals, readily soluble in organic solvents. The solubility in water was about 2.2 g per 100 g. M.p. 143-144°.

0.3500 g substance: 35.8 ml 0.05 N NaOH. 0.1780 g substance: 18.15 ml 0.05 N NaOH. Found: M 195.6, 195.9. $C_{10}H_{12}O_4$. Computed: M 196.2.

4-Ethoxyphenoxyacetamide was synthesized like the 4-methoxyphenoxyacetamide, the yield being 70.5%. 5.52 g of hydroquinone monoethyl ether and equimolar quantities of the other reagents yielded 5.5 g of the amide. M.p. 137° after recrystallization from water.

3. 4-Propoxyphenoxyacetic acid. Under the experimental conditions described above for the synthesis of 4-ethoxyphenoxyacetic acid, 7.6 g of hydroquinone monopropyl ether, 4.7 g of monochloroacetic acid, and 4.4 g of sodium hydroxide in 75 ml of water yielded – after suitable treatment – 7.1 g (67.6%) of 4-propoxyphenoxyacetic acid. The acid was purified by recrystallizing it from water. Readily soluble in organic solvents, about 0.1 g dissolving in 100 g of water. M.p. 108°.

0.1372 g substance: 13.1 ml 0.05 N NaOH. 0.1410 g substance: 13.4 ml 0.05 N NaOH. Found: M 210.3, 210.4. $C_{11}H_{14}O_4$. Computed M 210.2.

4-Propoxyphenoxyacetamide was synthesized with a yield of 78.5%. 7.6 g of hydroquinone monopropyl ether, 4.7 g of chloroacetamide, and 1.15 g of sodium in 30 ml of absolute alcohol yielded 8.8 g of the amide. The latter was purified by crystallizing it from 40% methanol. M.p. 134-135°.

4. 4-Butoxyphenoxyacetic acid. 6.6 g of hydroquinone monobutyl ether, 3.8 g of monochloroacetic acid, and 3.6 g of sodium hydroxide in 75 ml of water yielded 8 g (89%) of 4-butoxyphenoxyacetic acid. The acid was purified by recrystallizing it from 50% CH_3OH. A white crystalline substance, slightly soluble in water, readily soluble in organic solvents. M.p. 112°.

0.0809 g substance: 7.2 ml 0.05 N NaOH. 0.0752 g substance: 6.65 ml 0.05 N NaOH. Found: M 224.8, 226.0. $C_{12}H_{16}O_4$. Computed: M 224.2.

The amide of this acid was synthesized with a yield of 76.4%. It was purified by crystallization from 80% methanol. The melting point of the pure substance was 126-127°.

5. 4-Isoamoxyphenoxyacetic acid. Under the same conditions as in the preceding experiments, 7.2 g of hydroquinone monoisoamyl ether, 3.8 g of monochloroacetic acid, and 3.6 g of NaOH in 75 ml of water yielded 7.5 g (78%) of 4-isoamoxyphenoxyacetic acid. The acid was crystallized from 50% methanol. White crystals, slightly soluble in water. M.p. 124-125°.

0.0946 g substance: 7.8 ml 0.05 N NaOH. 0.0815 g substance: 6.8 ml 0.05 N NaOH. Found: M 242.0, 239.8. $C_{13}H_{18}O_4$. Computed: M 238.3.

The yield of 4-isoamoxyphenoxyacetamide was 75%. 7.2 g of hydroquinone monoisoamyl ether, 3.7 g of chloroacetamide, and 0.92 g of sodium in 30 ml of isoamyl alcohol yielded 7.3 g of the amide. M.p. 132° (from 60% CH_3OH).

6. 4-Methoxyphenoxy-α-butyric acid. 4.96 g of hydroquinone monomethyl ether and 7.84 g of ethyl bromobutyrate were added to a solution of sodium ethoxide prepared from 1.15 g of metallic sodium and 30 ml of absolute alcohol. The resultant mixture was boiled for two hours over a water bath in a flask fitted with a reflux condenser. After this time had elapsed, 25 ml of 10% NaOH was added to the reaction mixture, and heating was continued for another 10 minutes. Then 125 ml of water and 1 g of activated charcoal were added to the solution. The solution was filtered after being boiled for a short interval of time, and acidified with HCl

after it had cooled down. The oil that separated out was extracted with benzene, the benzene solution was desiccated with sodium sulfate, and the benzene was driven off. The oil crystallized after being kept for a long time at -12°. The crystals were pressed out and recrystallized from gasoline. B.p. 52°.

0.1205 g substance: 11.4 ml 0.05 N NaOH. 0.1278 g substance: 12.0 ml 0.05 N NaOH. Found: M 211.4, 211.3. $C_{11}H_{14}O_4$. Computed: M 210.2.

7. 4-Ethoxyphenoxy-α-butyric acid. 5.52 g of hydroquinone monoethyl ester, 7.84 g of ethyl bromobutyrate, and 1.15 g of sodium in 30 ml of absolute alcohol yielded 6.2 g (69.2%) of 4-ethoxyphenoxy-α-butyric acid, the experimental conditions being the same as those in Experiment 6. The m.p. was 79-80° after recrystallization from gasoline.

0.1525 g substance: 13.8 ml 0.05 N NaOH. 0.1175 g substance: 10.4 ml 0.05 N NaOH. Found: M 224.2, 225.9. $C_{12}H_{16}O_4$. Computed : M 224.2.

8. 4-Propoxyphenoxy-α-butyric acid. 6.08 g of hydroquinone monopropyl ester, 7.84 g of ethyl bromobutyrate, and 1.15 g of sodium in 30 ml of alcohol yielded 6.9 g (73.2 %) of 4-propoxyphenoxy-α-butyric acid, the experimental conditions being the same as those in Experiment 6. A white crystalline substance with a m.p. of 66°.

0.2322 g substance: 19.2 ml 0.05 N NaOH. 0.0315 g substance: 2.6 ml 0.05 N NaOH. Found: M 241.8, 238.4. $C_{13}H_{18}O_4$. Computed: M 238.3.

9. 4-Butoxyphenoxy-α-butyric acid. 6.6 g of hydroquinone monobutyl ether was dissolved in 75 ml of 5% sodium hydroxide, and 6.7 g of α-bromobutyric acid was added; the resulting mixture was heated for three hours over a boiling water bath. After the solution had cooled, it was acidulated with hydrochloric acid, and the oil that had separated out was extracted with benzene, the acid being extracted from the benzene with aqueous ammonia. Acidulating the ammoniacal solution caused the 4-butoxyphenoxy-α-butyric acid to settle out as an oil, which soon crystallized. The 4-butoxyphenoxy-α-butyric acid was purified by recrystallizing it from gasoline. The yield was 3.4 g (33.7%). A white crystalline substance, slightly soluble in water, but readily soluble in organic solvents. M.p. 70-71°.

We obtained a yield of 57.4% of 4-butoxyphenoxy-α-butyric acid when we synthesized it by the method described in Experiment 6. 6.6 g of hydroquinone monobutyl ether yielded 5.8 g of the acid.

0.0728 g substance: 5.76 ml 0.05 N NaOH. 0.1955 g substance: 15.4 ml 0.05 N NaOH. Found: M 252.7, 258.8. $C_{14}H_{20}O_4$. Computed: M 252.3.

10. 4-Isoamoxyphenoxy-α-butyric acid. 7.2 g of hydroquinone monoisoamyl ether, 7.8 g of ethyl bromobutyrate, and 1.15 g of sodium in 30 ml of alcohol yielded 6.8 g (63.6%) of 4-isoamoxyphenoxy-α-butyric acid, the experimental conditions being the same as those in Experiment 6. A white crystalline substance, slightly soluble in water, but readily soluble in organic solvents. M.p. 88°. We also synthesized this acid by the method described in Experiment 9. The yield was 22.5%.

0.3384 g substance: 25.0 ml 0.05 N NaOH. 0.0842 g substance: 6.3 ml 0.05 N NaOH. Found: M 270.0, 267.3. $C_{15}H_{22}O_4$. Computed: M 266.3.

SUMMARY

The following compounds, not hitherto described in the literature, have been synthesized: 4-ethoxy-, 4-propoxy-, 4-butoxy-, and 4-isoamoxyphenoxyacetic

acids and their amides; and methoxy-, ethoxy-, propoxy-, butoxy-, and isoamoxyphenoxy-α-butyric acids. The yields of all the foregoing compounds were quite satisfactory.

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Mar. 15, 1949

RSEARCHES ON ISOMERIC TRANSFORMATIONS

VIII. TRANSFORMATIONS OF DIMETHYLCYCLOPENTYLCARBINOL

S. S. Nametkin and M. A. Volodin

S.S.Nametkin and D.M.Gabriadze [1] have shown that the five-membered ring compound dimethylcyclopentylcarbinol is partially isomerized to a six-membered ring by the acid reagents, oxalic and hydrobromic acids. One of the products of dehydrating the carbinol proved to be 1,2-dimethylcyclohexene-Δ_1, while one of the bromides produced by reacting fuming hydrobromic acid with the carbinol was 1,1-dimethylcyclohexyl bromide.

The structures of all the products of these transformations of dimethylcyclopentylcarbinol were not established completely. In particular, the positions of the double bonds in the products of the dehydration of the carbinol by oxalic acid were not ascertained, nor was the structure of the unstable bromide or the position of the bromine in the stable bromide. As for the ring system to which they belonged, these problems were settled quite accurately, with the exception of the unstable bromide.

We set ourselves the task of repeating these transformations of dimethylcyclopentylcarbinol in order to make a more thorough study of the resulting products.

Our research indicated that dehydration of dimethylcyclopentylcarbinol by oxalic acid yields a mixture of naphthylenes, which was divided into two fractions by an initial distillation into a tower with an efficiency of 16 theoretical trays: Fraction I: 130-133°; Fraction II: 136.5-137° at 752 mm. The constants of both fractinns proved to be close to those of the fractions collected in the paper by S.S.Nametkin and D.M.Gabriadze. The constants of Fraction I also turned out to be close to those of the hydrocarbon prepared by B.A.Kazansky and G.T.Tatevosyan [2] by dehydrating the same carbinol.

Subsequent triple fractionation of Fraction I showed, however, that this fraction is a mixture, which we divided into two fractions:

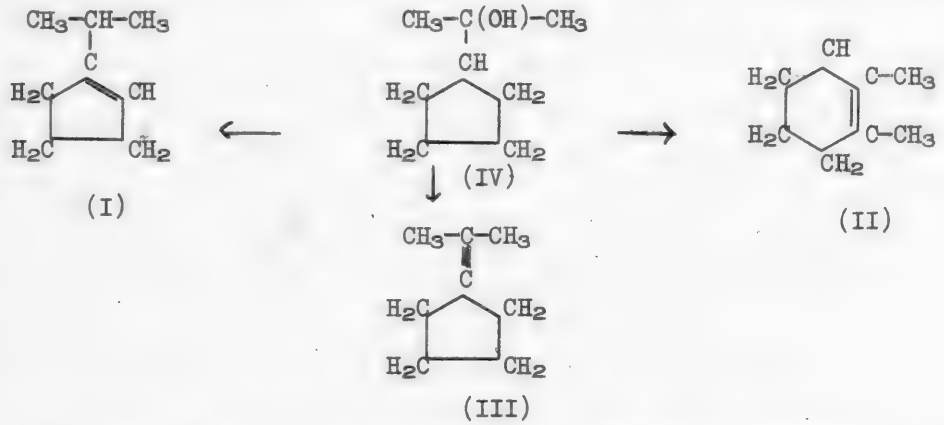
Fraction I: 123-123.2°; Fraction II: 136-137° at 745 mm.

Hydrogenation of the hydrocarbon in Fraction I (b.p. 123-123.2°) at 160° above platinum yielded a saturated hydrocarbon, isopropylcyclopentane, while oxidation of the naphthylene with potassium permanganate yielded a monobasic keto acid with the composition of $C_8H_{14}O_3$, γ-isobutyryl-n-butyric acid. B.A.Kazansky and G.T.Tatevosyan prepared the same acid by oxidizing their hydrocarbon from dimethylcyclopentylcarbinol.

Thus, hydrogenation as well as oxidation of the hydrocarbon in Fraction I, with a b.p. of 123-123.2°, corroborate the structure of the hydrocarbon as that of 1-isopropylcyclopentene-Δ_1.

The constants of the hydrocarbon in Fraction II (b.p. 136-137°) proved to be fairly close to those of the hydrocarbon in Fraction II (b.p. 134-138°) secured by S.S.Nametkin and D.M. Gabriadze when they dehydrated dimethylcyclopentylcarbinol; they identified its structure as that of 1,2-dimethylcyclohezene-Δ_1 by hydrogenation and ensuing bromination (preparing tetrabromo-o-xylene).

Theoretically, we might expect the dehydration of dimethylcyclopentylcarbinol (IV) to result in the formation of the following three hydrocarbons: 1-isopropylcyclopentene-Δ_1 (I); 1,2-dimethylcyclohexene-Δ_1 (II); and isopropylidenecyclopentane (III):



The constants of isopropylidenecyclopentane (III) resemble those of 1,2-dimethylcyclohexene-Δ_1 (II), and it is impossible to separate the two by fractionation, even into an efficient tower. It is, therefore, quite probable that the Fraction II we secured is a mixture of 1,2-dimethylcyclohexene-Δ_1 and isopropylidenecyclopentane. The higher molecular refraction of the hydrocarbon in Fraction II likewise points to the presence of a hydrocarbon with a semicyclic double bond in the mixture.

We investigated the hydrocarbon in Fraction II (b.p. 136-137°) two months after we had prepared it, beginning by redistilling it into a tower. This distillation indicated that much of the hydrocarbon had polymerized, changing its constants. The redistilled hydrocarbon (b.p. 138-139° at 770.5 mm) was oxidized with benzoyl peroxide; the resulting oxide was then hydrated. The resulting glycol fused at 64-65°, which is the melting point of the dimethyl tetramethylene glycol synthesized by Meerwein and Unkel [3]. The structure of the glycol we had prepared was definitely proved by dehydrating it with oxalic acid; this resulted in a ketone, the semicarbazone of which exhibited no depression of the melting point when mixed in a test sample with the semicarbazone of pure 1,1-dimethylcyclohexanone-2.

Thus, we may conclude from our investigations that the hydrocarbon with a b.p. of 138-139° was isopropylidenecyclopentane, whereas the hydrocarbon of Fraction II (b.p. 136-137°) secured immediately after dehydrating dimethylcyclopentylcarbinol with oxalic acid, was a mixture of isopropylidenecyclopentane and 1,2-dimethylcyclohexene-Δ_1. The presence of the latter in the dehydration products has

been proved beyond doubt by S.S.Nametkin and D.M.Gabriadze; in our experiment the 1,2-dimethylcyclohexene-Δ_1 polymerized after standing for a long time.

Hence, our research has confirmed the theoretically predicted structure of the hydrocarbons that are the dehydration products of dimethylcyclopentylcarbinol: 1-isopropylcyclopentene-Δ_1 (I); 1,2-dimethylcyclohexene-Δ_1 (II); and isopropylidenecyclopentane (III).

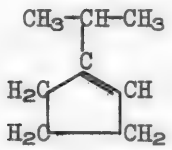
Our subsequent investigations have shown that the reaction of dimethylcyclopentylcarbinol with fuming hydrobromic acid yields a mixture of two bromides: a tertiary bromide, the product of the normal reaction, which is unstable under ordinary conditions; and a secondary bromide, 1,1-dimethyl-2-bromocyclohexane, a product with the isomerized ring system of the initial carbinol. Fractionation of this mixture in vacuum with a dephlegmator failed to separate the mixture into fractions, owing to the fact that the boiling points of the bromides lay extremely close together. The constants of the bromide mixture approximated the figures given in the literature for the stable bromide prepared by S.S.Nametkin and D.M.Gabriadze. This bromide mixture rapidly turned green upon standing, however, which indicated that it contained an unstable bromide. The bromide mixture was separated by boiling it for 30 to 40 minutes at atmospheric pressure until no more hydrogen bromide was evolved. Subsequent distillation yielded two fractions:

Fraction I: 130-145°; Fraction II: 191-192° at 762 mm. Fraction I contained a halogen and apparently represented a mixture of a hydrocarbon and vestiges of the tertiary bromide. Fraction II was double distilled in vacuum with a dephlegmator, after which it was a colorless liquid that did not change when kept for a long time.

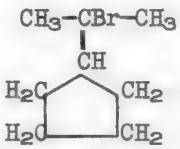
Fraction I (130-145°) was boiled with an alcoholic solution of an alkali to split off hydrogen bromide from the residual tertiary bromide, after which the mixture of naphthylenes was distilled into a tower with an efficiency of 16 theoretical trays. This distillation indicated that two fractions are collected when hydrogen bromide is detached from the unstable bromide:

Fraction I: 123-125°; Fraction II: 137-138° at 762 mm.

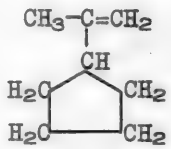
If the unstable bromide was a tertiary bromide, the product of the normal reaction of dimethylcyclopentylcarbinol with hydrobromic acid, as assumed by S.S. Nametkin and D.M.Gabriadze, the following hydrocarbons might be theoretically expected to result from the detaching of hydrogen bromide from it:



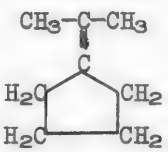
(I)



(IV)



(III)



(II)

Oxidizing the hydrocarbon of Fraction I with potassium permanganate yielded a keto acid, $C_8H_{14}O_3$, whose semicarbazone fused at 182.5-183°. A test sample, mixed

with the semicarbazone of the keto acid we had previously produced by oxidizing 1-isopropylcyclopentene-Δ_1, exhibited no depression of the melting point. Hence, it may be considered as established that the hydrocarbon of Fraction I was 1-isopropylcyclopentene-Δ_1 (I).

Oxidizing the hydrocarbon of Fraction II (b.p. 137-138°) with potassium permanganate yielded cyclopentanone, the semicarbazone of which exhibited no depression when mixed with the semicarbazone of pure cyclopentanone. This is convincing proof that the hydrocarbon of Fraction II was isopropylidenecyclopentane (III).

The third hydrocarbon (III) was not found in the mixture.

Thus, our investigations have shown that one of the products of the reaction of dimethylcyclopentylcarbinol with hydrobromic acid is a tertiary bromide that retains the five-membered ring system of the initial carbinol, is unstable under ordinary conditions, readily evolving hydrogen bromide and giving rise to two unsaturated hydrocarbons: isopropylidenecyclopentane – the product of the normal evolution of hydrogen bromide from the bromide – and 1-isopropylcyclopentene-Δ_1, which is apparently a product of the further transformation of the isopropylidenecyclopentane in an acid medium. The latter assumption is confirmed by the fact that the amount of Fraction II drops considerably when the bromide is boiled for a long time, the quantity of Fraction I rising accordingly.

In order to establish the structure of the second, stable bromide, the freshly distilled bromide was converted into the corresponding alcohol. The constants of the resultant alcohol proved to be close to the figures given in the literature for 1,1-dimethylcyclohexanol-2 [4]. The latter was converted into a ketone by oxidizing it with chromic acid mixture; the semicarbazone of the ketone fused at 196.5-197.5° and exhibited no depression of the melting point when mixed in a test sample with the semicarbazone of pure 1,1-dimethylcyclohexanone-2.

Thus, these transformations corroborate the structure of the stable bromide as being 1,1-dimethyl-2-bromocyclohexane. The results of our investigations agree fully with the structures proposed by S.S.Nametkin and D.M.Gabriadze for the bromides prepared by reacting dimethylcyclopentylcarbinol with fuming hydrobromic acid.

EXPERIMENTAL

Dimethylcyclopentylcarbinol

We prepared this carbinol from adipic acid as follows: distilling adipic acid with barium hydroxide yielded cyclopentanone; the cyclopentanone was converted into cyclopentanol by the Nenitzescu and Jonescu method [5]; a yield of 86% of cyclopentyl bromide, with a b.p. of 139-140° at 744 mm, was obtained by reacting the cyclopentanol with phosphorus tribromide; reacting solid carbon dioxide with cyclopentylmagnesium bromide, by the N.D.Zelinsky method, yielded cyclopentanecarboxylic acid, with a yield of 80%, which was then converted into its methyl ester; reacting methylmagnesium iodide with methylcyclopentanecarboxylate, by the Masson method, yielded dimethylcyclopentylcarbinol, the constants of which were:

B.p. 100-101° at 73 mm; d_4^{20} 0.9130; n_D^{20} 1.4591; MR_D 38.37.
Computed. $C_8H_{15}OH$ 38.46.

The constants of this carbinol were close to the figures given in the literature for the carbinol [1,2].

Dehydration of Dimethylcyclopentylcarbinol by Oxalic Acid

A mixture of 42 g of dimethylcyclopentylcarbinol and 126 g of crystalline oxalic acid was heated over a boiling water bath for 1.5 hours. Then a small amount

of water was added to the flask and the hydrocarbon was driven off with steam. The hydrocarbon was boiled with metallic sodium, after which it boiled at 130-135° at 744 mm. Then the hydrocarbon was distilled into a Vigreux fractionating column, with an efficiency of 16 theoretical trays.

The following major fractions were collected in the first fractionation at 752 mm:

Ia – 130-133°, 8.5 g; n_D^{20} 1.4525. IIa – 136-137°, 11.5 g; n_D^{20} 1.4593.

A second fractionation at 749 mm yielded the following results:

Ib – 122.5-123°, 7 g. IIb – 135-136°, 12 g.

Two sharp fractions were recovered in a third fractionation at 745 mm:

Ic – 123-123.2°; n_D^{20} 1.4443. IIc – 136.5-137°; n_D^{20} 1.4593.

Hence, the 130-133° fraction (first fractionation) was a mixture, even though its constants agreed with the figures for one of the dehydration products, 1-isopropylcyclopentene-Δ_1.

The physical properties of the dehydration products of dimethylcyclopentylcarbinol were as follows after triple distillation:

Fraction Ic: d_4^{20} 0.7988; n_D^{20} 1.4443; MR_D 36.64; Computed for $C_8H_{14}F$. 36.48.

Fraction IIc: d_4^{20} 0.8183; n_D^{20} 1.4593; MR_D 36.81; Computed for $C_8H_{14}F$. 36.48.

Analysis of the First Fraction of the Hydrocarbon with a B.P. of 123-123.2°

Hydrogenation of the hydrocarbon with a b.p. of 123-123.2°. 2 g of the unsaturated hydrocarbon was passed over a platinum catalyst at 160°. All the unsaturated hydrocarbon was converted into a saturated one after a single pass over the catalyst, the latter's constants being:

B.p. 124-124.5° at 742 mm; d_4^{20} 0.7762; n_D^{20} 1.4260;
Found: MR_D 37.01. Computed for C_8H_{16} – 36.94.

The constants of the hydrocarbon we prepared were very close to the figures given in the literature for isopropylcyclopentane.

Oxidation of the hydrocarbon with a b.p. of 123-123.2°. 1.65 g of the unsaturated hydrocarbon with a b.p. of 123-123.2° was shaken together with a 5% solution of potassium permanganate (4.75 g of $KMnO_4$ and 90.3 ml of water) in a bottle with a ground glass stopper. The permanganate was decolorized within two hours. The unreacted hydrocarbon was driven off with steam, and the aqueous solution was freed of the manganese dioxide and then evaporated to a volume of 3-4 ml, after which it was acidulated with dilute hydrochloric acid until it showed an acid reaction with tropeolin. The resulting oil was extracted with ether and, after the solvent had been driven off, mixed with a water-alcohol solution of 1 g of semicarbazide acetate. A white precipitate of a semicarbazone was thrown down at once; its m.p. was 182.5-183.5° when heated slowly. The melting point of this semicarbazone agrees with the melting point of the semicarbazone of the keto acid $C_8H_{14}O_3$ prepared by B.A.Kazansky and G.T.Tatevosyan [2] by oxidizing 1-isopropylcyopentene.

1.7 g of the semicarbazone with a m.p. of 182.5-183.5° was decomposed with dilute sulfuric acid (1:3). The semicarbazone decomposed even when left to stand at room temperature, its surface being covered with an oil, which was extracted with ether. After the solvent had been driven off, the residue was distilled in vacuum (with slight decomposition). This yielded 0.3 g of a colorless oil, which turned yellow upon standing:

B.p. 147-148° (10 mm); specific gravity was measured for the yellowed acid: d_4^{20} 1.0372; n_D^{20} 1.4439; MR_D 40.49; Computed for $C_8H_{14}O_3$ - 40.69.

Titration of the keto acid (yellowed after standing) yielded results that bore out the monobasic nature of the keto acid with the composition of $C_8H_{14}O_3$ (γ-isobutyryl-n-butyric acid), which might have been expected to result from the oxidation of 1-isopropylcyclopentene-Δ_1.

0.2093 g substance: 12.84 mg 0.1 N NaOH (13.05 ml theoretically).
Found M 160.7. Computed for $C_8H_{14}O_3$ - M 158.11.

Hence, both the hydrogenation and the oxidation of the hydrocarbon of Fraction I with a b.p. of 123-123.2° indicate that the structure of this hydrocarbon is 1-isopropylcyclopentene-Δ_1.

The appreciable difference between the constants we found for 1-isopropylcyclopentene-Δ_1 and the figures given in the literature for this hydrocarbon, as established by S.S.Nametkin and D.M.Gabriadze as well as by B.A.Kazansky and G.T. Tatevosyan, lead one to believe that the figures given in the literature do not apply to a wholly individual hydrocarbon. Obviously, triple fractionation into a tower enabled us to achieve a more complete separation of the naphthylenes - products of the dehydration of dimethylcyclopentylcarbinol.

This hypothesis is supported by the fact that our first fractionation yielded a product whose constants were close to those given in the literature for 1-isopropylcyclopentene-Δ_1.

Analysis of the Second Fraction of the Hydrocarbon With a B.P. of 136.5-137° (745 mm)

The second fraction of the unsaturated hydrocarbon, with a b.p. of 136.5-137° was analyzed two months after its preparation. Before analysis, this fractinn was redistilled into the same Vigreux fractionating column. Charge: 14 g; Fraction I - b.p. 138-139° at 770.5 mm - 8 g; Fraction II - b.p. above 139° (the bulk of it above 145°) - a yellow liquid.

Constants of Fraction I: d_4^{20} 0.8204; n_D^{20} 1.4597; MR_D 36.74;
Computed for C_8H_{14} 36.48.

As these figures indicate, the constants of the hydrocarbon of the second fraction of the products of the dehydration of dimethylcyclopentylcarbinol had changed after standing for two months, much of the hydrocarbon in this fraction having polymerized.

Oxidation of the hydrocarbon with a b.p. of 138-139° (770.5 mm). 7 g of the hydrocarbon with a b.p. of 138-139° was gradually added, with constant stirring, by the Prilezhaev method, to an ether solution (190 ml) of benzoyl hydrogen peroxide ($P_{act.oxygen}$ = 0.01142 in 2 ml of solution), after which the mixture was shaken up and left to stand for 4 days at room temperature. Determination of the excess benzoyl hydrogen peroxide after the four days had passed indicated that all the hydrocarbon had been oxidized. The benzoic acid was washed out of the ether solution with a dilute alkali and then with water. The solvent was driven off, and the residue was distilled. The resultant oxide has the following constants:

B.p. 151-154° at 755 mm; d_4^{20} 0.9041; n_D^{20} 1.4425; MR_D 36.95;
Computed for $C_8H_{14}O$ - 36.39.

Hydrating the oxide with a b.p. of 151-154° (755 mm). 3.5 g of the oxide with a b.p. of 151-154° was added a little at a time to acidulated water (4 ml of

water plus 2 drops of concentrated sulfuric acid). Agitating the mixture caused the oxide to dissolve at once, appreciable heat being evolved. Sometimes the mixture had to be chilled to prevent the temperature from rising above 45-50°. The reaction mass was saturated with potash and then extracted with chloroform. Driving off the solvent yielded a glycol that crystallized in the form of true prisms, with a m.p. of 64-65°.

The melting point of the glycol we had synthesized was close to the figure given in the literature for the glycol of isopropylidenecyclopentane, synthesized by Meerwein and Unkel by a different method (m.p. 61-63°).

Dehydration of the glycol with a m.p. of 64-65°. In order to reach a definite conclusion regarding the structure of this glycol, it was dehydrated as prescribed by Meerwein and Unkel.

2 g of pinacone, 20 ml of water, and 2 g of oxalic acid were distilled at a temperature of 150° over an oil bath. An oil was steam distilled, which was dissolved in methanol after it had been freed of water; then it was mixed with a water-alcohol solution of semicarbazide acetate. The precipitate of the semicarbazone was thrown down very quickly; it fused at 196-197° after crystallization from alcohol.

The melting point of the semicarbazone is that of the semicarbazone of 1,1-dimethylcyclohexanone-2. A test sample of the semicarbazone, mixed with the semicarbazone of pure 1,1-dimethylcyclohexanone-2, exhibited no depression of the melting point and fused at 195-196°.

Thus, we may conclude that the hydrocarbon with a b.p. of 138-139°, which was kept for two months, was isopropylidenecyclopentane.

Action of Fuming Hydrobromic Acid Upon Dimethylcyclopentylcarbinol

30 g of dimethylcyclopentylcarbinol was heated in a sealed tube with four times its volume of hydrobromic acid, saturated at 0°, for 5 hours at 100-105°.

The reaction mass was washed with water and desiccated over calcium chloride, after which it was distilled in vacuum:

B.p. 81-83° at 23 mm; d_4^{20} 1.2295; n_D^{20} 1.4895; MR_D 44.89;
Computed for $C_8H_{15}Br$ – 44.71.

The resulting bromide was a colorless liquid with a characteristic odor, which turned green very rapidly upon standing.

The bromide with a b.p. of 81-83° (23 mm) was boiled with a reflux condenser. The evolution of hydrogen bromide came to a stop after 30 minutes; the liquid had turned brown. It was then distilled at 762 mm:

Fraction I: 130-145°, 14 g (green).

Fraction II: 191-192°, 13 g (slightly yellowish).

The first fraction was washed to remove any traces of hydrogen bromide; it was found to contain a halogen. It was then saponified with an alcoholic alkali. The quantity of alkali used was such that 50% of this fraction was a bromide.

The fraction with a b.p. of 130-145° (762 mm) was boiled for 1 hour with 11 g of potassium hydroxide dissolved in 40 ml of ethyl alcohol. Steam distillation and boiling the product with sodium twice yielded 6.5 g of a hydrocarbon with a b.p. of 130-133° at 762 mm. This hydrocarbon was fractionated into a Vigreux column with an efficiency of 16 theoretical trays. Two major fractions were

collected in this first fractionation at 762 mm:

Fraction I: b.p. 123-125°; n_D^{20} 1.4443; d_4^{20} 0.7990; MR_D 36.63.
Computed for C_8H_{14} 36.48.
Fraction II: B.p. 137-138°; n_D^{20} 1.4597; d_4^{20} 0.8202; MR_D 36.70.
Computed for C_8H_{14} 36.48.

The constants of the fractions collected were close to those of the fractions collected during the dehydration of dimethylcyclopentylcarbinol with oxalic acid, the structure of which has been set forth above.

Oxidation of the hydrocarbon with a b.p. of 123-125° (762 mm). 2.4 g of the unsaturated hydrocarbon with a b.p. of 123-125° was oxidized with a 5% potassium permanganate solution (6.92 g of $KMnO_4$ to 131 ml of water), as previously described for the oxidation of the hydrocarbon with a b.p. of 123-123.2°.

The semicarbazone of the keto acid was prepared; it fused at 182.5-183° after being recrystallized from methanol. A test sample of this semicarbazone, mixed with the semicarbazone of the γ-isobutyryl-n-butyric acid synthesized by us and described earlier, exhibited no depression and fused at 182-183°.

Hence, the hydrocarbon with a b.p. of 123-125° was 1-isopropylcyclopentene-Δ_1.

Oxidation of the hydrocarbon with a b.p. of 137-138° (762 mm). 5.5 g of the unsaturated hydrocarbon was shaken together with a chilled 1% solution of potasskum permanganate (10.55 g of $KMnO_4$ to 1045 ml water). All the potassium permanganate was reduced within 40 minutes. The reaction mass was then distilled with steam. Two distillates were collected: 100 ml and 500 ml. Each distillate was concentrated to 5 ml and then mixed with a solution of semicarbazide acetate. With the first distillate the semicarbazone was thrown down at once; it fused at 200-202° after crystallization from water, followed by crystallization from methanol; this is the figure given in the literature for the semicarbazone of cyclopentanone. A test sample of this semicarbazone, mixed with the semicarbazone of pure cyclopentanone, exhibited no depression of the melting point, fusing at 200-203°.

The semicarbazone fused in a wide temperature range (174-195°) after its first crystallization from water; this is evidently due to contamination with acetone semicarbazone. We were unable to secure the latter in the pure state, however.

Thus, we may consider the structure of the hydrocarbon of Fraction II, with a b.p. of 137-138°, to be established as that of isopropylidenecyclopentane. The increased specific gravity of this hydrocarbon may be due to traces of unsaturated hydrocarbons with six-membered rings, which may have been formed from the stable bromide, in consequence of incomplete separation of the bromides.

Investigation of the stable bromide. The stable bromide, which boils at 191-192° under ordinary conditions, was twice distilled in vacuum:

B.p. 85.5° at 23 mm; d_4^{20} 1.2331; n_D^{20} 1.4902; MR_D 44.81.
Computed for $C_8H_{15}Br$. 44.71.

The bromide was a colorless liquid with a characteristic odor that underwent no change in prolonged storage.

The carbinol of the stable $C_8H_{15}Br$ Bromide. A stream of anhydrous oxygen was passed through a chilled ethereal solution of a Grignard reagent, prepared with 1.2 g of magnesium shavings and 9 g of the bromide with a b.p. of 85.5° (at 23 mm). Then the reaction mixture was decomposed, at first with water, and then with dilute

hydrochloric acid. The ether layer was washed and desiccated with fused potash. The ether was driven off, and the residue distilled in vacuum. This yielded 2 g of a carbinol:

B.p. 76-77° at 17 mm; d_4^{20} 0.9243; n_D^{20} 1.4648; MR_D 38.30;
Computed for $C_8H_{16}O$ 38.47.

The constants of the carbinol are close to those given in the literature for 2,2-cyclohexanol-1, produced by Meerwein by another method.

A higher-boiling fraction, with a b.p. of 155-156° (20 mm) was also collected; apparently, this was a hydrocarbon produced as a by-product in a Wurtz reaction.

Ketone from the carbinol with a b.p. of 76-77° (17 mm). 1.5 g of the carbinol with a b.p. of 76-77° was gradually added to a chromic acid mixture, prepared with 2.43 g of potassium bichromate, 2 g of concentrated sulfuric acid, and 13 ml of water. The temperature rose to 45°. After the temperature of the reaction mass had subsided, and all the potassium bichromate had been reduced, the mixture was distilled with steam. This yielded 0.7 g of a ketone, which was mixed with a solution of semicarbazide acetate. The semicarbazone was precipitated at once. Recrystallization from boiling methanol yielded the semicarbazone as fine needles that fused at 196.5-197.5°. A test sample, mixed with the semicarbazone of pure 2,2-dimethylcyclohexanone-1, exhibited no depression, fusing at 196-197°.

This indicates that the synthesized ketone is 2,2-dimethylcyclohexanone-1, that the carbinol we oxidized actually has the structure of 2,2-dimethylcyclohexa-ol-1, and that, therefore, the initial bromide was 1,1-dimethyl-2-bromocyclohexane.

SUMMARY

1. 1-isopropylcyclopentene-Δ_1; 1,2-dimethylcyclohexene-Δ_1; and isopropylidenecyclopentane have been prepared by eliminating water from dimethylcyclopentylcarbinol by means of oxalic acid.

2. Two bromides: a stable 1,1-dimethyl-2-bromocyclohexane, and an unstable dimethylcyclopentylbromomethane, which evolves hydrogen bromide and forms isopropylidenecyclopentane and 1-isopropylcyclopentene-Δ_1, have been prepared by reacting the above-mentioned alcohol with fuming hydrobromic acid.

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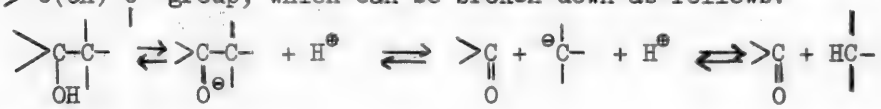
OXIDATIVE AND OXIDATIVE-HYDROLYTIC TRANSFORMATIONS OF ORGANIC MOLECULES

X. AMMONOLYSIS OF 2-CHLORO-2-METHYL-1, 3, 4-TRIOXOTETRALIN

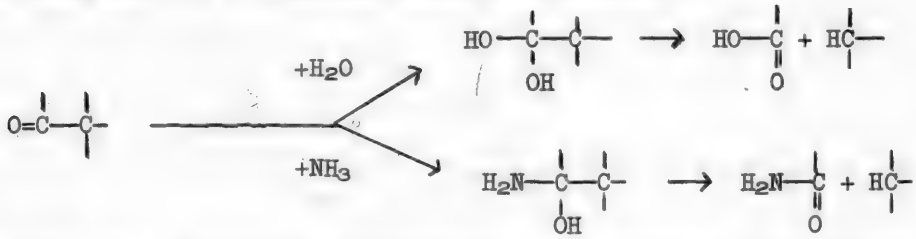
Yu. B. Shvetsov, I. A. Redkin and M. M. Shemyakin

In previously published papers [1-15], devoted to a study of the hydrolytic and oxidative-hydrolytic transformations of organic molecules, we have demonstrated that the process of opening carbon bonds under the action of hydrolytic agents is possible in those compounds that represent prototropic systems, containing the $>C(OH)-C-$ group, which can be broken down as follows:



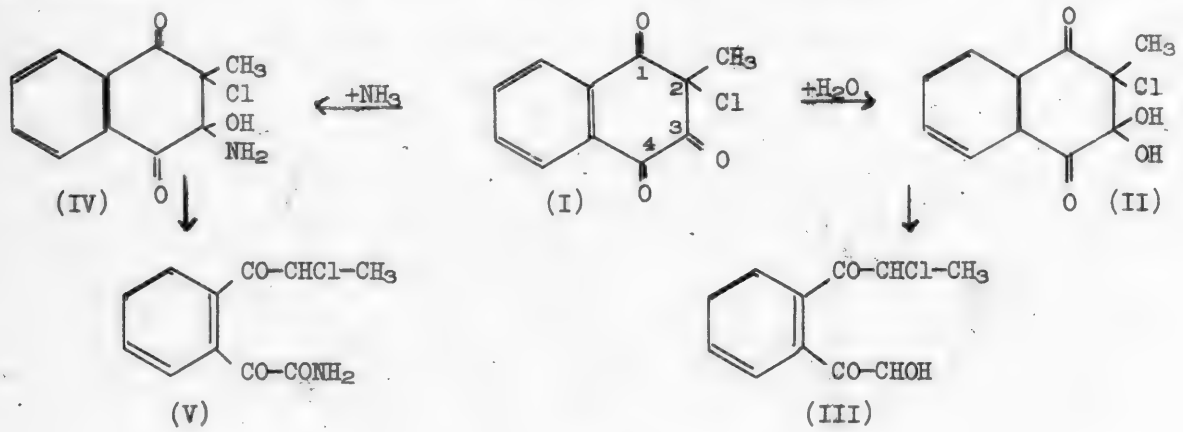
under certain conditions.

The hydrolytic cleavage of carbon bonds is also feasible in an extensive group of unsaturated cyclic and alicyclic compounds, as well as those containing a carbonyl group, inasmuch as many of them may be readily hydrated at the $>C=C<$ or $>C=O$ double bond, giving rise to the same $>C(OH)-C$ group. It was highly probable that in some types of carbonyl compounds the cleavage of the carbon bonds would prove to be feasible not only after the carbonyl group had been hydrated, but also after a molecule of ammonia had been added to them, since then the $>C(OH)-C-$ group might be expected to form. The nature of the terminal compounds produced as the result of hydrolysis or ammonolysis of the initial carbonyl compound would have to be somewhat different, however.



To check this hypothesis experimentally, we chose the chlorotrione (I), the hydration and hydrolytic cleavage of which were already known. We demonstrated

in Reports VII and VIII [13,14] that when this chlorotrione is reacted with water in the cold, it is converted very easily into compound (II), which quickly undergoes hydrolytic cleavage when boiled for a short time with water, or even without heating in an aqueous alkali solution, being transformed chiefly into o-(α-chloropropionyl)-phenylglyoxylic acid (III). The diagram given above would lead one to expect that carrying out a similar reaction in the presence of a concentrated aqueous solution of ammonia will subject the initial chlorotrione (I) to ammonolysis as well as hydrolysis, at first forming, in addition to the hydration product (II), compound (IV), which must then be transformed into the corresponding acid (III) and its amide (V) as the result of the ensuing cleavage of its cyclic groups. We secured both of the latter compounds by reacting the chlorotrione (I) with a 30% aqueous solution of ammonia, chilled to 0°, whence it follows that the bond between the 2 and 3 carbon atoms of its ring may undergo ammonolysis as well as hydrolysis.



Like the chlorotrione (I), its hydrated form (II) can also give rise to the acid (III) and the latter's amide (V) when reacted with a 25-30% aqueous solution of ammonia, whereas only the acid (III) is produced as a rule in dilute ammonia solutions. This indicates that when the ammonia concentration in the solution is rather high, the hydrated form of the chlorotrione (II) may undergo partial conversion into compound (IV), which is then cleaved to the amide (V). It should be noted that o-(α-chloropropionyl)-phenylglyoxylic acid (III) cannot be converted into the corresponding amide by reacting it with a 25-30% aqueous solution of ammonia. This example thus indicates that cyclic polyketones may undergo not only hydrolysis, but also ammonolysis of the ring carbon bonds.

o-(α-Chloropropionyl)-phenylglyoxylamide (V) is a white crystalline substance that fuses with decomposition at 234°. It can be converted into the o-(α-chloropropionyl)-phenylglyoxylic acid (III) previously described by us [13] by gradually adding a 10% aqueous solution of sodium nitrite to a boiling aqueous solution of the amide containing about 30% of sulfuric acid.* In the presence of

*No more than 40% of the o (α chloropropionyl) phenylglyoxylic acid (III) can be secured from the amide (V) under these conditions, since the formation of the acid (III) is always accompanied by the formation of a considerable amount of the lactone of o (α chloropropionyl) benzoic acid. The properties and structure of this latter compound will be described by us in our next report.

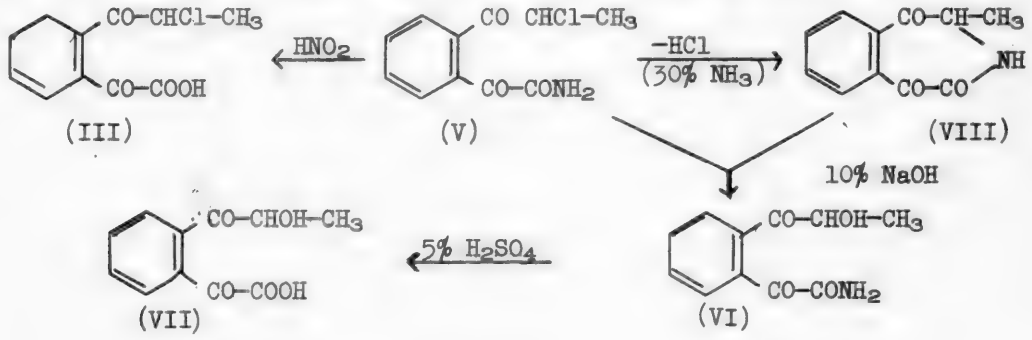
a 10% aqueous solution of caustic soda o-(α-chloropropionyl)-phenylglyoxylamide (V) is converted within 30 minutes at 18-20° into o-lactylphenylglyoxylamide (VI), which is quantitatively converted into the already known [10] o-lactylphenylglyoxylic acid (VII) by boiling for 4 hours with 5% sulfuric acid. These reactions are convincing proof of the structure we have assigned to the amide, as expressed by Formula V.

This amide undergoes very singular transformations when reacted with a 30% aqueous solution of ammonia at 30-40°. Hydrogen chloride is split off from the amide molecule (V), resulting in a nearly quantitative yield of a neutral compound with a m.p. of 189-190°, containing nitrogen, which has the empirical formula of $C_{11}H_9O_3N$, according to the analysis data; this formula is also in agreement with the results of the determinations of the substance's molecular weight. Comparison of the empirical formulas of the amide (V) and the substance with a m.p. of 189-190° ($C_{11}H_{10}O_3NCl$ and $C_{11}H_9O_3N$) indicates that the formation of the latter actually did entail the detachment of nothing but a molecule of hydrogen chloride from the initial amide (V). The ability of the compound with a m.p. of 189-190° to be converted very easily into the o-lactylphenylglyoxylamide (VI) described above when acted upon by a 10% aqueous solution of caustic soda at 18-20° indicates that this reaction does not involve any change in the molecule's carbon skeleton or in the nature of the oxygen-containing substituents.

These results lead to the supposition that the compound with a m.p. of 189-190° is a seven-membered lactam of o-alanylphenylglyoxylic acid (VIII), which is formed from the amide (V) by the intramolecular liberation of a molecule of hydrogen chloride. Weight is lent to this hypothesis by the fact that, in accordance with Formula (VIII), the substance with a m.p. of 189-190° possesses only one active hydrogen atom (as determined by the A.P.Terentyev method [18]). It is highly probable, therefore, that the compound we have synthesized actually possesses the structure expressed by Formula (VIII).

As we know, the lactam of ε-aminocaproic acid [17] is the simplest representative of this class of lactams with seven-membered rings. The properties of the compound we have synthesized differ very markedly, however, from that lactam in many respects. Whereas the lactam of ε-aminocaproic acid is converted into the corresponding amino acid by saponification, the lactam (VIII) is cleaved when reacted with an aqueous alkali solution, giving rise to o-lactylphenylglyoxylamide (VI) instead of o-alanylphenylglyoxylic acid. It is possible that this marked difference between the properties of these two lactams is due to the presence of carbonyl groups in the molecule of the lactam we have described.

In conclusion we should point out that the lactam (VIII) can be prepared otherwise than by reacting amide (V) with a concentrated solution of ammonia.



it can be secured by having the ammonia react with the chlorotrione (I) or its hydrate (II). The highest yield (up to 60%) is obtained by introducing the chlorotrione (I) into a 30% aqueous solution of ammonia. It is sufficiently obvious that in these instances the lactam (VIII) arises as a secondary product, namely, from the amide (V) produced by the ammonolysis of the chlorotrione (I) or of its hydrate (II).

EXPERIMENTAL *

1. Ammonolysis of the chlorotrione (I). 2.6 g of the chlorotrione (I)** was vigorously triturated with 6 ml of a 30% aqueous solution of ammonia, chilled to 0°, the reaction vessel likewise being chilled with ice water. A violent reaction set in almost at once, the liquid turning red-brown and a small precipitate being thrown down. The reaction came to a close within a few minutes; then the reaction mixture was diluted with 15 ml of water and acidulated, while chilled, with 10% sulfuric acid. This produced a rapidly solidifying red-brown mass. Weight 1.5 g. Double recrystallization from a small quantity of ethyl acetate (with some animal charcoal) yielded white crystals of the lactam of o-alanylphenyl glyoxylic acid (VIII), with a m.p. of 189-190°. The yield was 63%. (Cf Experiment 5 for the properties and transformations of this compound).

The acid reaction solution was repeatedly extracted with ether, and the ether solution was washed several times with a 10% soda solution and then with water. The washed ether solution was desiccated with sodium sulfate and boiled with animal charcoal, after which the ether was driven off. There remained 0.15 g (5%) of the white crystals of o-(α-chloropropionyl)-phenylglyoxylamide (V); the amide fused with decomposition at 234° after having been recrystallized from water (its properties and transformations are described in Experiment 3). The soda solution was acidified with 10% sulfuric acid and triple-extracted with ether. The ether solution was desiccated with sodium sulfate and boiled with animal charcoal, and the ether was driven off. There was left 0.47 g of a light yellow oil, which rapidly solidified into a white crystalline mass of the monohydrate of o-(α-chloropropionyl)-phenylglyoxylic acid (III). Its m.p. was 96° after recrystallization from dichloroethane [13]. The yield was 16%.

2. Ammonolysis of 2-chloro-2-methyl-1,2,3,4-tetrahydronaphthalenediol-3,3-dione-1,4 (II). 3 g of the finely powdered hydrated chlorotrione (II) (cf [13] for its preparation) was added in several batches to 5 ml of a 25% aqueous solution of ammonia. The substance dissolved quickly, the temperature rising slightly and a white crystalline precipitate being thrown down from the orange solution within 1-2 minutes. The reaction mass was diluted with 20 ml of water and acidulated, while chilled, with 30% sulfuric acid. The precipitate was filtered out and washed with water. This yielded 1.05 g of o-(α-chloropropionyl)-phenylglyoxylamide (V), with a m.p. of 215-220° (with decomp.). The substance fused at 234° with decomposition after having been recrystallized once or twice from water, using animal charcoal. After the amide precipitate had been filtered out, the reaction solution was triple-extracted with ether, and the ether solution was washed repeatedly with a 10% soda solution and then with water.***The pH of the reaction solution was raised to 5-5.5 by adding soda, and then the solution

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* The analytical portion of this research was carried out with the assistance of E. A. Ignatyeva, to whom we are deeply indebted.

** The chlorotrione (I) was prepared from its hydrate (II) under conditions that have been described in detail in one of our previous reports [19].

*** 1.3 g (40%) of the monohydrate of o-(α-chloropropionyl)-phenylglyoxylic acid (VII) with a m.p. of 96° (from dichloroethane) can be extracted from the soda solution with ether.

was evaporated to dryness at 30° in vacuum. The dry residue was extracted with ether in a Soxhlet apparatus, using the previously obtained ether extract that had been washed with soda for the extraction. Boiling the ether solution with animal charcoal and driving off the ether yielded 0.4 g of a white crystalline substance with a m.p. of 170-180°, which was a mixture of the amide (V) and the lactam (VIII). Recrystallization from a small quantity of ethyl acetate yielded 0.15 g of the amide (V), the total quantity of which thus amounted to 1.2 g. Yield: 40%. After filtering out the amide, the mother liquor was evaporated to a volume of 2 ml; this precipitated 0.15 g of the lactam (VIII) as white crystals with a m.p. of 185-190°, which fused at 189-190° after being recrystallized from 1 ml of ethyl acetate. Yield: 6%.

3. Properties and transformations of o-(α-chloropropionyl)-phenylglyoxylamide (V). The amide (V) is a white crystalline substance that melts with decomposition at 234° (from water). It is readily soluble in alcohol and in hot water, but only slightly so in ether.

Found %: C 55.29; H 4.35; N 5.66; Cl 14.93. $C_{11}H_{10}O_3NCl$. Computed %: C 55.12; H 4.18; N 5.85; Cl 14.87. The number of active hydrogen atoms, as determined by the Terentyev method [16] (in pyridine) was 3.56 and 3.57.

Conversion to o-(α-chloropropionyl)-phenylglyoxylic acid (III). 0.5 g of the amide (V) was dissolved by heating it in 60 ml of 30% sulfuric acid, and 15 ml of a 10% aqueous solution of sodium nitrite was added a little at a time to the boiling solution during the course of 15 minutes, the nitrite being introduced through a pipet extending to the bottom of the flask. Gas was liberated violently, and the solution gradually turned cloudy. A white crystalline precipitate settled when the solution had cooled. It was filtered out and washed with water. Weight: 0.2 g. M.p. 80-81° (from 50% alcohol). The substance was insoluble in an aqueous soda solution, contained chlorine, and did not contain nitrogen.* The filtrate was triple-extracted with ether, and the ether solution was desiccated with sodium sulfate and boiled with animal charcoal, after which the ether was driven off. There remained 0.2 g of o-(α-chloropropionyl)-phenylglyoxylic acid (III), with a m.p. of 96° (from dichloroethane). The yield was 40%.

Conversion into o-lactylphenylglyoxylamide (VI). 1 g of the amide (V) was dissolved in the cold in 8 ml of a 10 solution of caustic soda, and the yellow solution was left to stand for 30 minutes at a temperature of 18-20°. Acidulation with 10% sulfuric acid threw down a white crystalline precipitate of o-lactylphenylglyoxylamide (VI), which was filtered out and washed with water. Weight: 0.8 g. M.p. 199° (from water). Yield: 80%.

Conversion into the lactam of o-alanylphenylglyoxylic acid (VIII). 0.5 g of the amide (V) was placed in 5 ml of a 30% solution of aqueous ammonia, and the mixture was gradually heated to 40° for 15 minutes. As heating progressed, the flocculent deposit of the original amide was gradually converted into the heavy, finely crystalline deposit of the lactam (VIII), which settled on the bottom of the flask. The reaction mixture was allowed to cool, and the precipitate was filtered out and washed with water. This yielded 0.4 g (94%) of a perfectly pure substance with a m.p. of 189-190°, which exhibited no depression of the melting point when mixed with the lactam prepared in Experiment 1.

*Cf our next report for the properties and structure of this substance, which proved to be the lactone of o-(α-chloropropionyl)-benzoic acid.

4. Properties and transformations of o-lactylphenylglyoxylamide (VI). The amide (VI) is a white substance that crystallizes as a monohydrate from water, with a m.p. of 199°. The amide is soluble in hot ethyl acetate, but insoluble in ether or benzene.

Found %: C 55.14; H 5.19; N 5.93; H_2O 7.65. $C_{11}H_{11}O_4N \cdot H_2O$. Computed %: C 55.23; H 5.44; N 5.86; H_2O 7.53. The number of active H atoms, as determined by the Terentyev method [16] (in pyridine) equals 4.99 and 5.00.

Conversion to o-lactylphenylglyoxylic acid (VII). 0.5 g of the amide (VI) was boiled for 4 hours with 20 ml of 5% sulfuric acid. After the solution had cooled, the pH of the solution was made 1-2, and it was evaporated to dryness at 35° in vacuum. The dry residue was extracted with ether in a Soxhlet apparatus for 15 hours. Driving off the ether yielded 0.46 g of a white crystalline substance, which had a m.p. of 231° (with decomp.) after having been recrystallized from water with animal charcoal. It fused at the same temperature with decomposition when mixed with o-lactylphenylglyoxylic acid [19]. The yield was nearly quantitative.

5. Properties and transformations of the lactam of o-alanylphenylglyoxylic acid (VIII). The lactam (VIII) is a white crystalline substance with a m.p. of 189-190°, which is readily soluble in most of the ordinary organic solvents (ether, alcohol, chloroform, and benzene). It crystallizes readily from water or ethyl acetate. It turns yellow when exposed to light.

Found %: C 65.27; H 4.42; N 7.00. $C_{11}H_9O_3N$. Computed %: C 65.02; H 4.43; N 6.90. Number of active H atoms, as determined by the Terentyev method [16](in pyridine): 1.15 and 1.17. Cryoscopic determination of the molecular weight in nitrobenzene: Found: M 202. $C_{11}H_9O_3N$. Computed: M 203.

Conversion to o-lactylphenylglyoxylamide (VI). 0.3 g of the lactam (VIII) was triturated at 18-20° with 3 ml of a 10% caustic soda solution. The substance dissolved gradually, a transparent yellow solution being produced within 10 minutes. Acidulating the solution with a 10% sulfuric acid solution precipitated the white crystalline amide (VI), which was filtered out, washed with water. Weight 0.3 g (81%). M.p. 198-199°. The substance fused at the same temperature when mixed with the o-lactylphenylglyoxylamide prepared in Experiment 3.

SUMMARY

A tetrahydronaphthalene chlorotrione (I) has been used as an example to demonstrate the feasibility of ammonolyzing the carbon bonds of cyclic polyketones. Cleavage of the ring of this chlorotrione yielded: o-(α-chloropropionyl)-phenylglyoxylic acid and its amide, as well as the seven-membered lactam of o-α-anylphenylglyoxylic acid. Several of the properties and transformations of the last two compounds have been investigated. It has been found that the lactam is a secondary product, formed from the o-(α-chloropropionyl)-phenylglyoxylamide by reacting the latter with an excess of concentrated aqueous ammonia.

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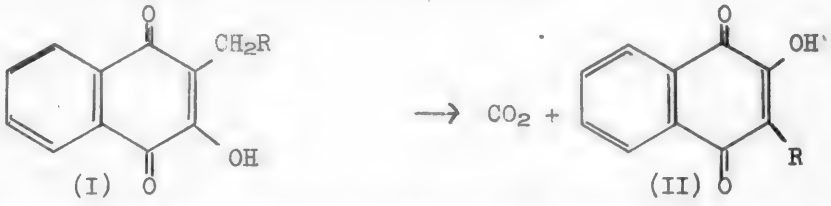
*See CB translation as follows: p.165, p. 175, p. 419, p. 431, p. 447, p. 457.

OXIDATIVE AND OXIDATIVE-HYDROLYTIC TRANSFORMATIONS OF ORGANIC MOLECULES

XI. THE MECHANISM OF THE S. HOOKER REACTION

L. A. Shchukina, Yu. B. Shvetsov and M. M. Shemyakin

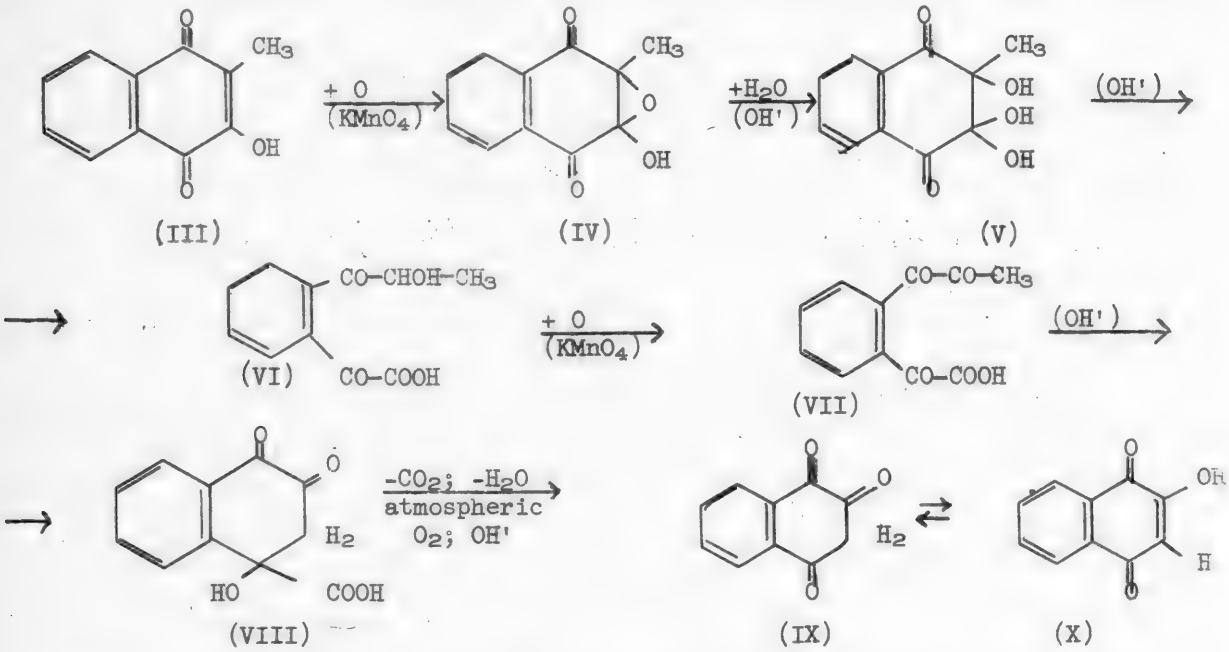
In 1936 S.Hooker discovered [1] that in the presence of an alkaline solution of potassium permanganate 2-alkyl-(as well as 2-alkenyl)-3-hydroxy-1,4-naphthoquinones of the general type (I) can undergo quite singular transformations, resulting in formation of hydroxynaphthoquinones of type (II):



As the above diagram indicates, this reaction involves not only a shortening of the side chain of the original quinone by one methyl group, but also a shift of the substituent along the quinone ring of the molecule; this second factor has been rigorously demonstrated by L.Fieser [2]. The latter, as well as S.Hooker, devoted considerable time to a study of the mechanism of these extremely unusual transformations, which appear inexplicable at first glance. Both of these research workers came to the conclusion that processes of this sort must entail opening of the quinone ring, followed by a reclosing of the ring, though they differed in their interpretations of the mechanism underlying the intermediate steps of the reaction [3,4]. The hypothetical diagrams they advanced remained without experimental confirmation, so that the problem of the mechanism of the reaction discovered by S. Hooker has not been solved in any satisfactory manner (cf [5] for details).

In connection with the new concepts of the nature of the oxidative and oxidative-hydrolytic transformations of organic molecules involving cleavage of the carbon bonds that have been developed by us in recent years, we undertook a study of the mechanism of the S.Hooker reaction in our laboratory some years ago, beginning with the simplest representative of the quinones of type (I), namely: 2-methyl-3-hydroxy-1,4-naphthoquinone (phthiocol) (III). As a result of this research, we were able by 1946 not merely to make an experimental study of the major stages of this reaction, but to elucidate the nature of the process as a whole [5,6,18]. We found that the conversion of phthiocol (III) into 2-hydroxy-1,4-naphthoquinone (X) takes place in accordance with the subjoined diagram and is the consequence of the simultaneous action of the oxidant (potassium permanganate and atmospheric oxygen)

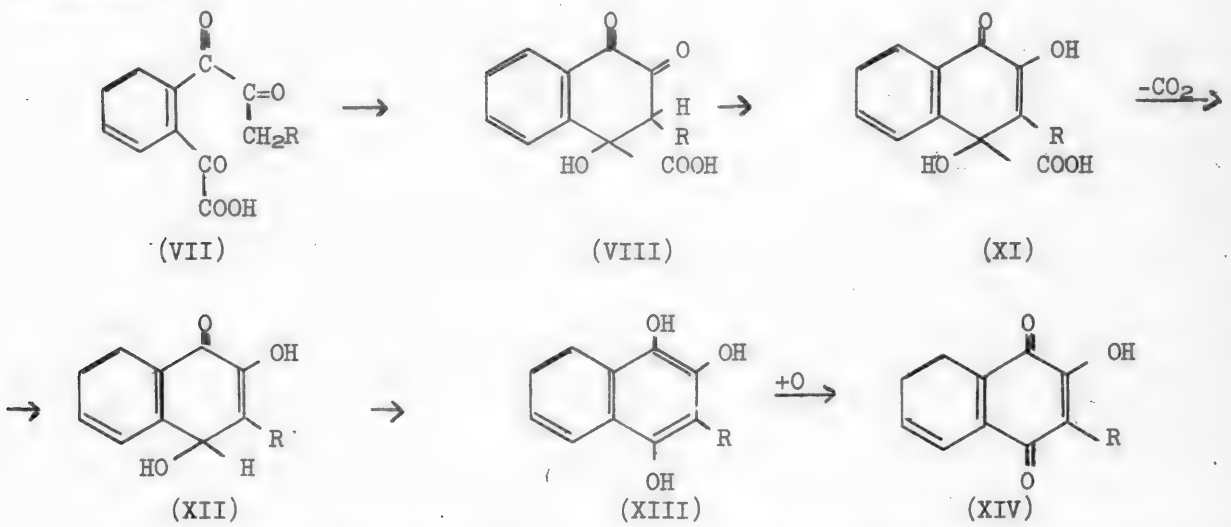
and the aqueous alkali solution (which exerts a hydrolyzing as well as condensing effect) upon the original molecule and the intermediate compounds.



The correctness of the first stage of these transformations [(III) → (IV) → (V) → (VI)] is indicated by the fact that glycol (V), which we synthesized by a different method, proved to be capable of being converted, under the usual conditions of the S.Hooker reaction, into, first, the hydroxydiketo acid (VI), and then into the end product, 2-hydroxy-1,4-naphthoquinone [5,6]. The second stage of the diagram [(VI) → (VII)] was substantiated as follows: on the one hand, we were able to isolate the triketo acid (VII) directly from the reaction solution [5] by interrupting the oxidation of the original hydroxynaphthoquinone (III) at a certain stage of the process; and on the other, we proved [5] that this triketo acid (VII) is also formed when the hydroxy diketo acid (VI) is oxidized by potassium permanganate in a S.Hooker reaction. Lastly, we were likewise able to make a study of the third stage [(VII) → (VIII) → (IX) ⇄ (X)], owing to our managing to divide the S.Hooker reaction, stopping it artificially at the stage in which the triketo acid (VII) is formed. It was found that the latter compound can be converted into the final 2-hydroxy-1,4-naphthoquinone (X) in an aqueous alkali solution only when an oxidant is present (such as atmospheric oxygen); we discovered [5,7] that the triketo acid (VII) first forms the cyclic α-hydroxy acid (VIII) which can be converted into the final hydroxyquinone, like some other α-hydroxy acids of the same type, only by oxidative decarboxylation. With all these facts as a basis, we were able to suggest, as far back as 1946, the diagram set forth above as an explanation of the S.Hooker reaction.

Toward the end of 1948, L. and M.Fieser published new material dealing with this reaction, [8]. Their subsequent investigations had compelled them to abandon the diagram they had proposed previously [3], the incorrectness of which had also been demonstrated by us [5]. At the same time they advanced another diagram to explain the mechanism of the S.Hooker reaction, which agreed in the main with the

diagram we had proposed and which is set forth above. The first stage of this diagram, dealing with the formation of hydroxydiketo acids of type (VI) was not investigated experimentally by L. and M. Fieser. They did express the supposition, however, that these acids are probably formed from the original quinones via a stage in which intermediate type (V) compounds are formed. As for this, all we need say is that the origin of compounds of this sort at that stage of the process, as well as their ability to be converted subsequently into Type (VI) hydroxy diketo acids had already been proved experimentally by us, using phthiocol (III) as a model [5]. The second stage of the diagram proposed by L. and M. Fieser coincides completely with the corresponding part of our diagram, and, moreover, we had already demonstrated, beyond any doubt, by the example of phthiocol (III), the formation in this stage of Type (VI) hydroxy diketo acids and their subsequent conversion into Type (VII) triketo acids as the result of oxidation by potassium permanganate. Inasmuch as L. and M. Fieser had been able to isolate a Type (VI) hydroxy diketo acid as an intermediate in the oxidation of lapachol by a S. Hooker reaction, their new data serves as additional confirmation of the correctness of the diagram set forth above. As for the transformation of Type (VII) triketo acids into the terminal Type (X) hydroxynaphthoquinones, this final portion of the L. and M. Fieser diagram which differs considerably from our diagram, is largely wrong. L. and M. Fieser, who did not isolate the intermediate Type (VII) triketo acids in a single one of the cases they investigated and did not study the properties of these acids, hypothetically pictured the subsequent course of their transformations, basing their arguments solely upon some quite farfetched analogies. Correctly believing that an aqueous alkali solution first cyclizes these triketo acids to the corresponding Type (VIII) α-hydroxy acids (cf the foregoing diagram, as well as [5,7]), L. and M.Fieser advanced, however, an incorrect diagram for their subsequent transformations:



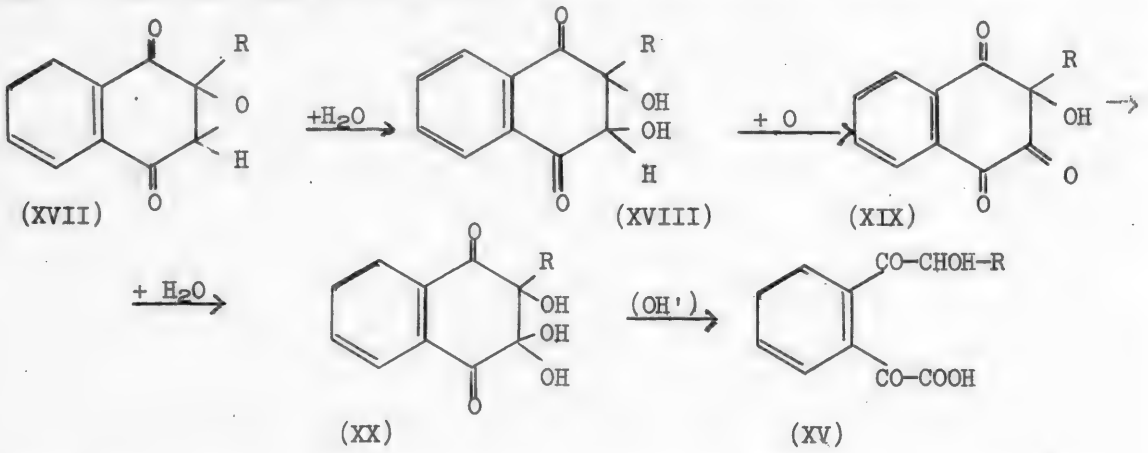
According to L. and M. Fieser, Type (VIII) hydroxy acids are first isomerized to Type (XI) hydroxy acids, which, as vinyl analogs of β-keto acids, are decarboxylated by an aqueous alkali solution alone. As they see it, the latter process is also promoted by the tendency of Type (XII) compounds to be aromatized to Type (XIII) hydroquinones, which are then oxidized to the final hydroxynaphthoquinone (XIV). In fact, the process of decarboxylation takes place only when the reaction is carried

out in an aqueous alkali solution with an oxidant present, such as atmospheric oxygen.

As we have shown [5,7], Type (VIII) cyclic α-hydroxy acids, which are formed, for example, by ring closure in the hydroxy diketo acid (VI) and the triketo acid (VII), can undergo only oxidative decarboxylation, whence it follows that the notions of L. and M.Fieser concerning the mechanism of this stage of the S. Hooker reaction are false.

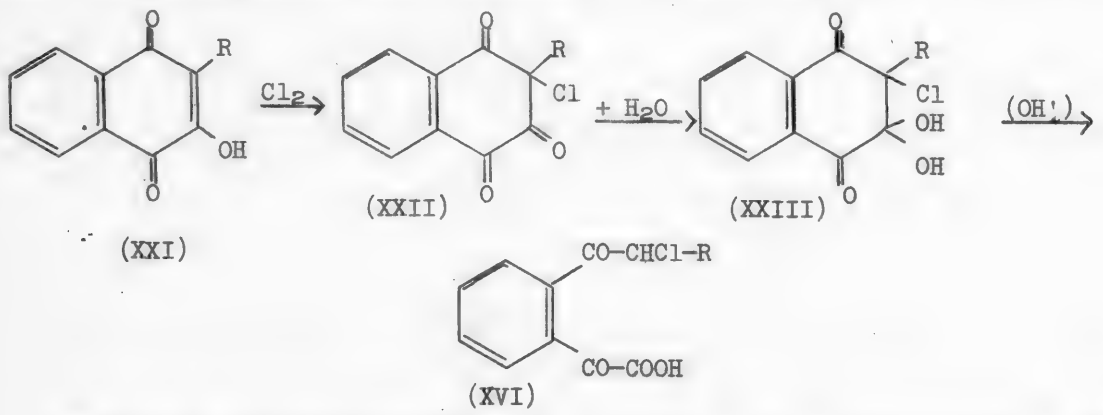
This paper by L. and M. Fieser [8] touches on a number of other questions that also demand special consideration, inasmuch as the experimental data set forth by us in our previous reports clear up the fundamental nature of some of the reactions described by them.

Several years ago [6,7,9,10,18,19] we suggested two simple methods for synthesizing presently unknown types of compounds with the general formulas of (XV) and (XVI), and at the same time cleared up the mechanism of the reactions involved in their formation. Type (XV) compounds can be produced by the oxidative-hydrolytic cleavage of naphthoquinone oxides (XVII):



(XVII) (XVIII) (XIX) (XX) (XV)

Type (XVI) compounds are readily synthesized from 3-hydroxy-1,4-naphthoquinones, containing various substituents at the 2 position:



(XXI) (XXII) (XXIII) (XVI)

We are now using these methods to synthesize certain representatives of Type (XV) and Type (XVI) substances.

Toward the end of 1948 L. and M. Fieser published [8] a different method of preparing these compounds, using substituted hydroxynaphthoquinones of the Type (XXI) as their starting substances. L. and M. Fieser converted the latter into compounds with the general formula of (XV) by reacting them with hydrogen peroxide in a soda solution, and converted these same hydroxynaphthoquinones into compounds with the general formula of (XVI) by reacting them with sodium hypochlorite in a soda solution. The mechanism of these two reactions was not investigated, except for the brief mention [8] of the supposition, which was not supported experimentally, that the formation of Type (XV) hydroxy diketo acids may possibly take place via a Type (XX) intermediate compound. Comparison of the results of our earlier researches [6,7,9,10] with the data of L. and M. Fieser leaves no doubt of the fact that the mechanism of the reactions they described is similar to that of the processes we have studied, represented schematically above. As shall be shown later, the conversion of Type (XXI) hydroxyquinones into Type (XV) and Type (XVI) compounds discovered by L. and M. Fieser is a typical example of oxidative-hydrolytic reactions, which take place not only as the result of the action of hydrogen peroxide or sodium hypochlorite, but also as the result of a high pH of the medium.

In fact, it is well known by now that the action of alkaline solutions of hydrogen peroxide (and some other oxidizing agents) upon the quinones results in the formation of oxides of these quinones, which can be converted into the corresponding glycols with very great ease at pH values higher than 7 for the solution.* It follows that under the conditions described by L. and M. Fieser, the formation of Type (XX) glycols constitutes the first stage of the transformation of the hydroxy quinones (XXI) into Type (XV) hydroxy diketo acids. On the other hand, we had previously found [6] that these glycols cannot exist if the solution pH is higher than 7, since they then undergo hydrolytic cleavage at the instant they are formed, being converted into the very hydroxy diketo acids (XV) that have been discovered by L. and M. Fieser. Hence, the second stage of the reaction they have described boils down to the hydrolytic cleavage of the intermediate glycol (XX) by the soda solution, the reaction as a whole being a variant of our method of synthesizing hydroxy diketo acids (XV), starting out with quinone oxides (XVII) (cf the diagram illustrated above).

As for the reaction published by L. and M. Fieser involving the formation of chloro diketo acids of the general type (XVI), produced by reacting sodium hypochlorite and soda solutions with hydroxyquinones (XXI), the general character of this reaction and its mechanism are practically the same as the method previously proposed by us for synthesizing compounds of this type (cf diagram). The sole difference is that L. and M. Fieser carried out this reaction without subdividing it into its separate stages, whereas we performed it in several stages, thus being able to ascertain the mechanism of the reaction. As we have shown [10], the action of chlorine on hydroxyquinones (XXI) results in the formation of Type (XXII) chlorotriones if no water is present, which are then hydrated by water at once, even in the cold, being converted into compounds of the general type of (XXIII). The latter may also be formed directly, by effecting the chlorination in the presence of water. It was likewise established that Type (XXIII) compounds tend very much to hydrolytic cleavage: they are converted practically instantaneously into chloro diketo acids of the general type of (XVI) when the solution pH exceeds 7, some of them being cleaved even when the pH is 7. This explains why L. and M. Fieser secured precisely these chloro diketo acids when they reacted solutions of hypochlorite and soda with (XXI) hydroxynaphthoquinones. It is obvious that the mechanism of the reaction described by L. and M. Fieser is essentially the same as the mechanism of the reaction we had investigated earlier.

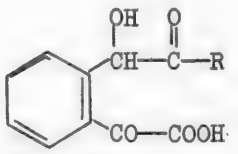
*The literature references on this topic are cited in our previous reports [5,6].

Lastly, we must spend some time on the problem of the structure of hydroxy diketo and chloro diketo acids of the general types of (XV) and (XVI), inasmuch as L. and M. Fieser have made statements on this subject [8] that are not entirely obvious and that are contradicted by the data set forth below.

In our previous reports [5-7,9-11] we showed that the properties of such acids (especially, their tendency to be converted into bicyclic compounds of the tetrahydronaphthalene series and even into quinones) is in agreement with the structural formulas (XV) and (XVI). It was also pointed out that these acids may also exist in the tautomeric forms (XXIV) and (XXV).

X = OH (XV); X = Cl (XVI); X = OH (XXIV); X = Cl (XXV).

Moreover, it is rather probable that hydroxy diketo acids can react in still another tautomeric form under certain conditions, namely, as compounds with the general formula of (XXVI):



(XXVI)

L. and M. Fieser made a study of some of the properties of hydroxy diketo and chloro diketo acids and came to the conclusion [8], however, that these compounds must be assigned structures expressed by Formulas (XXVII) and (XXVIII), while the tautomeric conversions of substances of this sort must be confined, according to them, to the formation of only the forms (XV) and (XVI) under certain conditions. *

X = OH (XXVII); X = Cl (XXVIII). X = OH (XV); X = Cl (XVI).

L. and M. Fieser reached these conclusions on the basis of the following experimental observations. They found that some hydroxy diketo acids and their esters could form diacyl derivatives as well as monoacyl derivatives and monosemicarbazones. Moreover, they discovered that in some instances they were able to secure two isomeric monoacyl derivatives of esters of these hydroxy diketo acids. At the same time they demonstrated that chloro diketo acids and their esters can form monoacyl derivatives. This led L. and M. Fieser to conclude that the molecules of the hydroxy diketo acids they were investigating must each contain two hydroxyl groups and one each of the carbonyl and carboxyl groups, whereas the molecules of

*L. and M. Fieser also discussed the possibility of an oxylactone (lactol) structure of the compounds in question. They rightly rejected this supposition on the grounds that, in contrast to aldehydic and keto acids, which possess a suitable structure and form two series of esters (α- and φ-), hydroxy diketo and chloro diketo acids always give rise to only one type of ester, according to L. and M. Fieser [8], no matter what the conditions governing the preparation of the latter. We have published similar results [7]

the chloro diketo acids must contain one hydroxyl, one carbonyl, and one carboxyl group. They proposed the structural formulas (XXVII) and (XXVIII) to explain these facts.

It must be emphasized, however, that these facts can be interpreted quite satisfactorily without the assumptions made by L. and M. Fieser. Owing to the work of A.E.Favorsky and his pupils, especially T.I.Temnikova, it is well known by now that α-ketols can exist and react in the following three tautomeric forms under certain conditions:*

It is therefore quite natural to suppose that these hydroxy diketo acids and their esters, which are α-ketols, likewise may tend to react in similar forms, namely: (XV), (XXIV), and (XXVI), of which the endiol form (XXIV) can form diacyl derivatives (cf [12]), while the forms (XV) and (XXVI) give rise to two different, though isomeric, monoacyl derivatives (cf [15,16], as well as the corresponding monosemicarbazones. On the other hand, the following tautomeric conversions are possible with the α-chloro ketones, and hence with the chloro diketo acids under consideration here (cf the new experimental data cited by us below):

It follows that chloro diketo acids and their esters can react in form (XVI) or in form (XXV), the latter form, of course, giving rise to the corresponding monacyl derivatives under the proper conditions. Hence, the data described by L. and M. Fieser [8] and cited above are far from a sufficient basis for assigning structures expressed by the formulas (XXVII) and (XXVIII) to the hydroxy diketo and chloro diketo acids, respectively, since all the properties of these acids can be readily understood if we take the structural formulas (XV) and (XVI) as our starting point and allow for the possibility of keto-enol tautomerism in such compounds.

The results of the spectrographic analyses made by L. and M. Fieser [8] likewise prove that the structural formulas (XV) and (XVI) are correct. They discovered that the spectrographic characteristics of the hydroxy diketo and chloro diketo acids they had synthesized, as well as of their esters (with the exception of their diacyl and some of the monoacyl derivatives) greatly resemble the spectrographic characteristics of acetophenone and, especially, benzoin and desyl chloride, but differ sharply from the spectrographic data for the oxide of 2-methyl-1,4-naphthoquinone. These results indicate quite definitely that the atom groupings -CO-CH(OH)- and -CO-CHCl-, contained in the molecules of benzoin and desyl chloride, are also present in the molecules of hydroxy diketo and chloro diketo acids; this is further confirmation of the structural formulas (XV) and (XVI) proposed for these compounds.

L. and M. Fieser treat these same spectrographic data differently, however. Assuming that tautomeric conversions of the keto-enol type are out of the question in benzoin and desyl chloride, L. and M. Fieser consider the results of their spectrographic analyses as proof that the molecules of hydroxy diketo and chloro diketo acids contain a carbonyl group in an α-position to the aromatic ring, this

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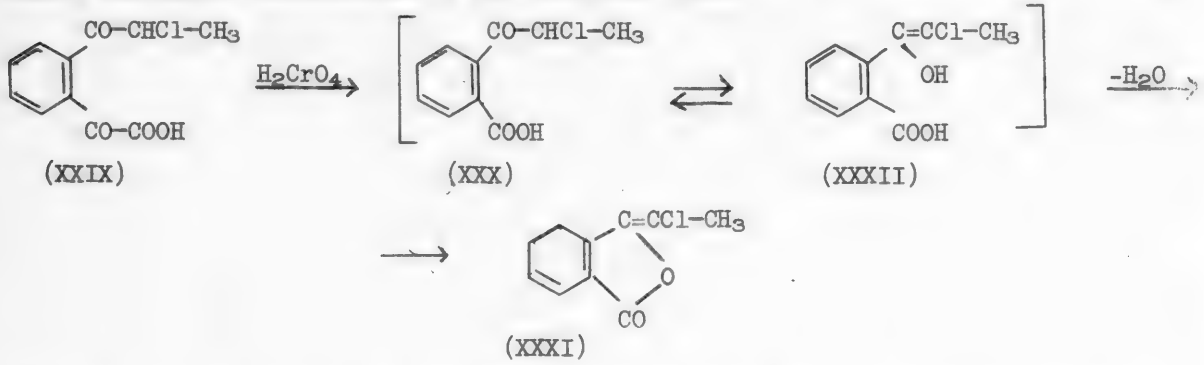
*The literature and the contemporary status of this problem are discussed in detail in some of T. I. Temnikova's recent papers [15, 16, 17].

group being unable to undergo partial or total enolization as a matter of principle. This leads them to conclude that the formulas (XXVII) and (XXVIII) (which do not contain an enolizing carbonyl group) advanced by them are correct, asserting that "benzoin is the best available model" in support of their point of view (cf [8], p. 3219-3220). But when we bear in mind the well-known (though ignored by L. and M. Fieser) tendency of substituted benzoins and aliphatic-aromatic α-ketols toward keto-enol tautomerism (cf the literature cited above), and allow for the fact that benzoin and desyl chloride are much closer structurally to Type (XV) and Type (XVI) compounds than to Type (XXVII) and Type (XXVIII) bicyclic α-hydroxy acids, it is hard to regard the comparison adduced by L. and M. Fieser as convincing. Nor is it superfluous to remark that of all the substances studied by L. and M. Fieser, the only one that doubtless contains non-enolizing carbonyl groups was 2-methyl-1,4-naphthoquinone; and its spectrographic curve proved to be quite different from the spectrographic curves of the hydroxy diketo and chloro diketo acids and from their derivatives. Hence, the assertion by L. and M. Fieser that these compounds must possess the structures expressed by Formulas (XXVII) and (XXVIII) must be regarded as unproved.

In conclusion we must discuss our new experimental data, which serve as further support of the correctness of Formulas (XV) and (XVI), which contain the $-C_6H_4-CO-CH(OH)-R$ and $-C_6H_4-CO-CHCl-R$ groups, since, in any event, we have succeeded in proving beyond doubt that keto-enol isomerism is possible in these compounds.

We have found that the o-(α-chloropropionyl)-phenylglyoxylic acid (XXIX), described previously [10], which is the simplest representative of acids with the general formula of (XVI), can be readily oxidized by chromic acid to o-(α-chloropropionyl)-benzoic acid (XXX), which proved, however, to be capable of existing only as a lactone (XXXI). The latter compound is a lactone of the enolic form of o-(α-chloropropionyl)-benzoic acid (XXXII), whence it follows that substances that contain the $-C_6H_4-CO-CHCl-R$ group may sometimes exhibit a very pronounced tendency toward tautomeric conversions of the keto-enol type.



(XXIX) (XXX) (XXXII) (XXXI)

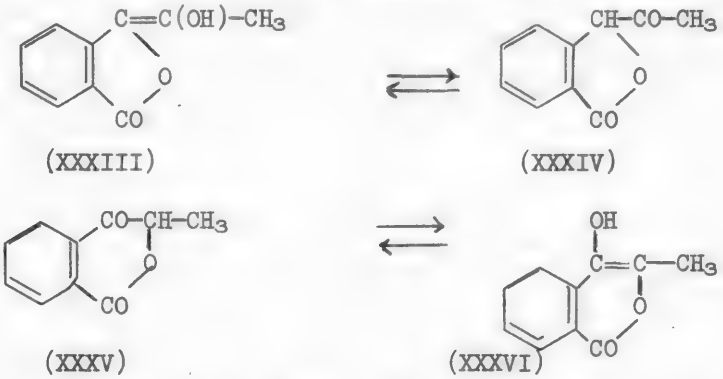
The lactone (XXXI) can also be synthesized from the o-(α-chloropropionyl)-phenylglyoxylamide described in our preceding report [13], by gradually adding an aqueous solution of sodium nitrite to a boiling aqueous solution of this amide containing about 30% of sulfuric acid.

The lactone we have synthesized is a white crystalline substance with a m.p. of 80-81°. Its composition is given by the empirical formula $C_{10}H_7O_2Cl$. Its molecule contains no active hydrogen atoms (as determined by the Terentyev method). The substance is insoluble in an aqueous soda solution, but dissolves slowly in

dilute solutions of caustic soda and more quickly in concentrated caustic soda solutions. This causes the original lactone to undergo several profound changes, a chlorine atom, in particular, being released; that is why this lactone can no longer be recovered in unchanged form when the alkaline solution is acidulated. Iodoform is produced by the action of a soda solution of hypoiodite upon the lactone. All these properties, together with the manner in which this compound is formed, prove beyond doubt that it possesses the structure expressed by Formula (XXXI).

Like o-(α-chloropropionyl)-phenylglyoxylic acid (XXIX), the o-lactylphenylglyoxylic acid (VI) we synthesized previously [7], which is the simplest representative of acids having the general formula of (XV), can also yield the corresponding lactone when oxidized by chromic acid, though, to be sure, the resulting yield of the lactone is minute, inasmuch as most of the original acid undergoes a much more far-reaching change. It is preferable to prepare this lactone from the o-lactylphenylglyoxylamide described in our preceding report [13]; as much as 40% of the lactone may be secured by dissolving this amide in 30% sulfuric acid and gradually adding a solution of sodium nitrite to the boiling solution. We discovered still another way of synthesizing this lactone, namely: by cautiously oxidizing o-propionylphenylglyoxylic acid (cf [14] for its preparation) with chromic acid. Here, the oxidation of the α-ketocarboxylic group to a carboxylic group is accompanied by the entrance of a hydroxyl group into the propionyl residue, which finally results in the formation of o-lactylbenzoic acid, which then yields the corresponding lactone as the result of ring closure.

The properties of this lactone are very similar to those of lactone (XXXI). It is a white crystalline substance with a m.p. of 101-102°. Its composition is that of the empirical formula $C_{10}H_8O_3$. The lactone is insoluble in an aqueous soda solution, but it is soluble in aqueous caustic soda; this rapidly causes far-reaching changes in the lactone, and to recover the initial lactone unchanged the alkaline solution must be acidified as soon as the substance has dissolved. Iodoform is produced by the action of a solution of hypoiodite in soda upon the lactone. These results agree with the finding that the lactone contains one active hydrogen atom (determined by the Terentyev method). All these properties, together with the way in which the lactone was synthesized, enable us to assign it the structure expressed by the formulas (XXXIII) $\rightleftarrows$ (XXXIV), by analogy with the lactone (XXXI). It is not impossible, however, that it has a six-membered lactone ring – Formulas (XXXV) $\rightleftarrows$ (XXXVI) – instead of a five-membered ring.



(XXXIII) (XXXIV)

(XXXV) (XXXVI)

Thus, consideration of all the data accumulated at the present time concerning the properties and transformations of hydroxy diketo and chloro diketo acids, described by us as well as by L. and M. Fieser, forces upon one the conclusion that

the structural formulas (XXVII) and (XXVIII) proposed for these compounds cannot be regarded as possessing experimental backing. All the known properties of compounds of this sort can be readily understood if we start out with the structural formulas (XV) and (XVI) we have put forward previously; moreover, it should be remembered that hydroxy diketo and chloro diketo acids may exhibit a tendency toward keto-enol tautomerism.

EXPERIMENTAL *

1. Preparation of the lactone of o-(α-chloropropionyl)-benzoic acid. a) 2.95 g of o-(α-chloropropionyl)-phenylglyoxylic acid (cf [10] for its preparation) was dissolved in 190 ml of 10% sulfuric acid, and a solution of 1.8 g of chromic anhydride in 10 ml of 10% sulfuric acid, chilled to +2°, was added to the resulting solution, chilled to the same temperature. The temperature of the mixture was gradually raised to 18-20° during the course of five hours. This caused the reaction liquid to turn gradually darker, becoming dark brown, a white crystalline precipitate settling out of the solution. A few drops of sodium bisulfite solution were added to the reaction mixture, and the dark-green solution was extracted with ether five times, without removing the precipitate that had formed. The ether solution was washed several times with a 10% soda solution and desiccated with sodium sulfate, and then the ether was driven off. This left 1.1 g (50%) of the lactone of o-(α-chloropropionyl)-benzoic acid in the form of white crystals, which fused at 80-81° after having been recrystallized from 50% alcohol. The soda solution was acidulated with 10% sulfuric acid and extracted five times with ether. The ether solution was desiccated with sodium sulfate, and the ether was driven off. This yielded 0.3 g (16%) of phthalic acid, with a decomp. temp. of 201° (from water). No phthalic acid was found in the reaction products.

b) 3.3 g of o-(α-chloropropionyl)-phenylglyoxylamide (cf the preceding report [13] for its preparation) was dissolved by heating it in 400 ml of 30% sulfuric acid, and 100 ml of a 10% aqueous solution of sodium nitrite was gradually added in small batches to the boiling solution via a pipet extending to the bottom of the flask. The solution gradually turned turbid, with drops of oil collecting at the bottom of the flask. The reaction was complete within 15-20 minutes. After it had cooled, the resulting lactone of o-(α-chloropropionyl)-benzoic acid crystallized. It was filtered out and washed with water.** Weight: 1.35 g. The substance fused at 80-81° after being recrystallized from 50% alcohol and exhibited no depression of the melting point when mixed with a sample of the lactone prepared in the preceding experiment. The yield was 50%.

2. Properties of the lactone of o-(α-chloropropionyl)-benzoic acid. The lactone is a white substance that crystallizes as hexagonal platelets with a m.p. of 80-81° from 50% alcohol.

> Found %: C 61.42; H 3.88; Cl 17.90. $C_{10}H_7O_2Cl$. Computed %: C 61.69; H 3.59; Cl 18.25. The molecular weight was determined cryoscopically in nitrobenzene. Found: M 188, 189. The lactone molecule has no active H atom [the determination was made by the Terentyev method (in pyridine)]. Computed M: 194.5.

The lactone is readily soluble in most organic solvents. It is insoluble in an aqueous soda solution and dissolves very slowly in a 0.1 N aqueous solution of caustic soda, but it dissolves quickly in a 1 N solution of caustic soda at 18-20°, undergoing farreaching changes as it does so. Chlorine is evolved quantitatively within a few minutes, and the original lactone can no longer be recovered by acidulating such a solution.

* E.A. Ignatyeva has assisted in the analytical portion of these investigations, for which we are deeply indebted to her.

** A considerable quantity of o-(α-chloropropionyl)-phenylglyoxylic acid may be recovered from the filtrate; it is produced from the initial amide together with the lactone (cf [13]) and does not undergo any other changes during the present reactions.

Lieben reaction. 0.2 g of the lactone was dissolved in 15 ml of methanol; a solution of 1 g of iodine in 8 ml of a 20% aqueous solution of potassium iodide and 10 ml of a 10% soda solution were added. The mixture was boiled for 15 minutes, after which it was cooled, and the resulting yellow crystalline precipitate of iodoform was filtered out and washed with water. Weight: 0.06 g (15%). M.p. 119°

3. Preparation of the lactone of o-lactylbenzoic acid. a) 3.2 g of o-lactylphenylglyoxylamide (cf [13] for its preparation) was dissolved by heating it in 60 ml of 30% sulfuric acid, and 35 ml of a 20% aqueous solution of sodium nitrite was added to the solution in small batches in the course of 10-15 minutes through a pipet extending down to the bottom of the flask. After the solution had cooled, its pH was made equal to 1, and the solution was evaporated in vacuum at 35° without removing the white crystalline precipitate The dry precipitate was treated repeatedly with cold acetone, and the latter was driven off. There remained 2.65 g of a white crystalline substance, which was a mixture of o-lactylphenylglyoxylic acid and the lactone of o-lactylbenzoic acid. These two substances were separated by heating the precipitate with benzene, in which only the lactone is soluble. This yielded 1.7 g (57% of o-lactylphenylglyoxylic acid with a decomp. temp. of 230° (from water) [7] and 0.95 g (40%) of the lactone of o-lactylbenzoic acid, with a m.p. of 101-102° (from water).

b) 1 g of o-lactylphenylglyoxylic acid was dissolved in 100 ml of 10% sulfuric acid, and a solution of 0.8 g of chromic anhydride in 15 ml of 10% sulfuric anhydride, chilled to -3°, was added to the first solution, chilled to the same temperature. The temperature of the solution was slowly raised to 14° during the course of 3 hours. The solution's color changed gradually, becoming brown by the time the reaction came to a close. A few drops of a sodium bisulfite solution were added to the reaction mixture, and the resulting green solution was extracted five times with ether. The ether solution was washed several times with a 10% aqueous solution of soda and then with water, and desiccated with sodium sulfate, after which the ether was driven off. There was left 0.01 g of a white crystalline substance that fused at 101-102° after recrystallization from ether and exhibited no depression of the melting point when mixed with a sample of the lactone of o-lactylbenzoic acid prepared in the preceding experiment. The yield was 1.3%.

The soda solution was acidified with 10% sulfuric acid and then extracted with ether. Desiccating the ether solution with sodium sulfate and driving off the ether yielded 0.05 g (6%) of phthalic acid with a decomposition temp. of 202° (from water). After the phthalic acid and the lactone of o-lactylbenzoic acid had been extracted from the reaction liquid, the solution pH was made equal to 1. Then the solution was evaporated to dryness in vacuum at 20°, and the dry residue was extracted with ether for 10 hours in a Soxhlet apparatus. Driving off the ether yielded 0.4 g of a colorless, thick, oily substance, which proved to be phthalonic acid.* This substance was dissolved in 15 ml of water, and 0.5 g of o-phenylenediamine, dissolved in 15 ml of water, was added to the solution. After several hours had elapsed, a finely crystalline precipitate of the o-phenylenediamine salt of the quinoxaline derivative of phthalonic acid settled out. The next day a 10% solution of caustic soda was added to the mixture in excess, causing the previously precipitated deposit to dissolve completely. The o-phenylene diamine was extracted from the alkaline solution with ether, after which air was blown through the alkaline solution to remove the ether, and, lastly, the solution was acidulated with 10% sulfuric acid until its reaction was lightly acid with

*To isolate and identify phtalonic acid it is best to secure it as its quinoxaline derivative, described in one of our previous reports [5], which is onli slightly soluble in water. This method, extensively used in several of our investigations, is useful whenever minute quantities of phthalonic acid are associated in a mixture with phthalic acid, as well as with some other acids.

Congo red. The crystalline white precipitate was filtered out and washed with water Weight: 0.3 g. M.p. 225-228°. Recrystallization from alcohol yielded a substance with a m.p. of 238-239°, which was identical with the previously described quinoxaline derivative of phthalonic acid [5]. A test sample, mixed with a specially prepared sample of this compound, fused at the same temperature. The yield of phthalonic acid was 25%.

c) 0.75 g of o-propionylphenylglyoxylic acid (cf [14] for its preparation) was dissolved in 30 ml of 10% sulfuric acid, and 0.6 g of chromic anhydride dissolved in 5 ml of 10% sulfuric acid chilled to -5° was added to the solution, chilled to the same temperature. The reaction solution was allowed to stand for 3 hours, the temperature gradually being raised to 15°. This caused the solution to darken very quickly, finally becoming blackish-green. When the reaction was over, the solution was extracted five times with ether, and the ether extract was washed with a 10% soda solution and with water, after which the ether was driven off. There remained 0.15 g of an oily substance, which rapidly solidified into a crystalline mass. Recrystallization from water, using animal charcoal, yielded white crystals with a m.p. of 101°, which fused at the same temperature when mixed with the lactone of o-lactylbenzoic acid prepared in Experiment 3a. The yield was 23%.

The soda solution was acidulated with 10% sulfuric acid and then extracted five times with ether. The ether solution was desiccated with sodium sulfate, and the ether was driven off. There was left 0.13 g (22%) of phthalic acid with a decomp. temp. of 198-200° (from water). After the aqueous reaction solution had been extracted with ether, it was evaporated to dryness in vacuum at 40°, the solution pH first having been made equal to 1. The dry residue was extracted with ether for 16 hours in a Soxhlet apparatus. Driving off the ether yielded 0.12 g (16%) of the unreacted original acid as white crystals with a m.p. of 173° (from water).

4. Properties of the lactone of o-lactylbenzoic acid. The lactone is a white substance that crystallizes from water as fine needles with a m.p. of 101-102°

Found %: C 67.96; H 4.71. $C_{10}H_8O_3$. Computed %: C 68.18; H 4.54. The number of active hydrogen atoms, as determined by the Terentyev method (in pyridine), is 1.53 and 1.29.

The lactone is readily soluble in most organic solvents. It is insoluble in an aqueous soda solution, but it dissolves quickly at 18-20° in a 0.1 N solution of caustic soda. The original lactone may be extracted with ether with a yield that does not exceed 50%, provided the resulting alkaline solution is quickly acidified with sulfuric acid. After remaining in the alkaline solution for a long time, the lactone undergoes far-reaching changes and can no longer be recovered by acidulating the solution.

Lieben reaction. 0.2 g of the lactone was dissolved in 8 ml of 50% methanol, a solution of 1 g of iodine in 5 ml of a saturated aqueous solution of potassium iodide and 15 ml of a 10% soda solution was added. The mixture was boiled for 10 minutes, after which it was cooled, and the yellow precipitate of iodoform was filtered out and washed with water. Weight: 0.08 g (18%). M.p. 119°.

SUMMARY

1. It has been shown that the scheme for the mechanism of the S. Hooker reaction proposed by L. and M. Fieser, which agrees in the main with the scheme earlier advanced by us, is erroneous as far as the decarboxylation of bicyclic α-hydroxy acids and their transformation into the final hydroxynaphthoquinones are concerned.

2. It has been found that insofar as their mechanism is concerned, the reactions described by L. and M. Fieser for the formation of the hydroxy diketo and chloro diketo acids (XV) and (XVI) are identical with the methods for synthesizing these compounds previously proposed by us.

3. It has been demonstrated that all the properties of this kind of hydroxy diketo and chloro diketo acids, described by us as well as by L. and M. Fieser, may be readily understood if the structural formulas (XV) and (XVI) are taken as the starting point; it must be borne in mind that these acids may display a tendency toward keto-enol tautomerism. The structural formulas of the (XXVII) and (XXVIII) types proposed by L. and M. Fieser for these acids must be considered to be without experimental support at the present time.

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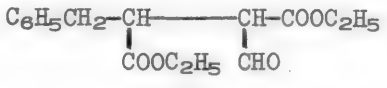
*See CB translation as follows: p. 419, p. 447, p. 165, p. 175, p. 431, p. 457, previous article, p. 1323.

THE SYNTHESIS OF α-BENZYLPARACONIC ACIDS

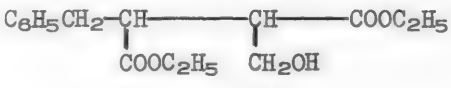
B. M. Mikhailov

The method developed by A.E.Chichibabin and N. A. Preobrazhensky for preparing pilopic acids [1] was used for the synthesis of α-benzylparaconic acids.

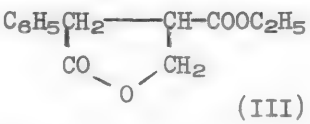
Ethylformylbenzyl succinate (I) was prepared, with a yield of some 60%, by condensing ethylbenzyl succinate with ethyl formate. Reducing (I) with amalgamated aluminum in a Wislicenus reaction [2] yielded ethylbenzyl itamalate (II), which gave up a molecule of alcohol when distilled in vacuum, being converted into an ester of lactonic acid – a mixture of stereoisomeric ethyl-α-benzyl paraconates (III):



(I)



(II)



(III)

Fractionation of this mixture separated it into two esters: a liquid ester with a b.p. of 171-172° at 0.6 mm, and a solid ester with a b.p. of 180-182° at 0.6 mm and a m.p. of 45.5-46°.

In contrast to the α-phenylparaconic esters [3], these esters are fairly stable. They yield two racemic acids when saponified. The liquid ester yielded α-benzylparaconic acid with a m.p. of 102-103°; while the solid ester yielded an acid with a m.p. of 134.5-135°. Like the ethylparaconic acid from the corresponding ester [1], the acid from the solid ester proved to be unstable, for when it was heated to 180-200°, all of it turned into the acid prepared by saponifying the liquid ester.

EXPERIMENTAL

Synthesis of ethylformylbenzyl succinate. A mixture of 50 g of ethylbenzyl succinate (b.p. 175-176° at 9 mm) and 18 g of ethyl formate was added to sodium ethoxide in ether, prepared with 5 g of sodium and 10 g of absolute alcohol, chilled with ice. The reaction mixture was set aside to stand for two days at a temperature of 0-2° and another 5 days at room temperature. Then the reaction mass was decomposed with ice, the ether layer was removed, and the aqueous layer was twice extracted with ether. The aqueous solution of the sodium salt of the formylbenzylsuccinic ester was chilled and then acidulated with dilute sulfuric acid. The resulting

product was extracted with ether, and the ether solution was washed with water and desiccated with sodium sulfate. Driving off the ether left 32.7 g of an oil – 59.5% of the theoretical quantity of ethylformylbenzyl succinate. Ethylformylbenzyl succinate was not isolated in subsequent tests, its ether solution being reduced directly.

Preparation of α-benzylparaconic esters. The crude ether solution of the ethylformylbenzyl succinate was reduced with amalgamated aluminum by the Wislicenus method [2]. Reduction is considerably faster when the mixture is heated to 25° and a small amount of water is added. The reaction mixture was left to stand overnight to ensure that reduction was complete. Then the ether solution was decanted, the aluminum hydroxide was washed repeatedly with ether, the ether solution was desiccated, and the ether was driven off. This yielded 32.5 g of ethylbenzyl itamalate. The total of 88 g of ethylbenzyl itamalate prepared in several runs was then distilled. Distillation at reduced pressure resulted in splitting off alcohol, which was collected and identified. Then the benzylparaconic esters were distilled at 12.5 mm (b.p. 213-223° at 12.5 mm; 72.8 g).

Repeated fractionation of the mixture of benzylparaconic esters yielded the following fractions (at 0.6 mm); 1) 171-172°, 20 g; 2) 172-174°, 17.5 g; 3) 174-180, 18.8 g; and 4) 180-182°, 5.4 g.

The 171-172° (0.6 mm) fraction was a liquid ester.

n_D^{20} 1.5150; d_0^{20} 1.1562; MR_D 64.73; computed: 64.36.
0.1221 g substance: 0.3029 g CO_2; 0.0715 g H_2O. Found %: C 67.64; H 6.55. $C_{14}H_{16}O_4$. Computed %: C 67.72; H 6.50.

The 180-182° (0.6 mm) fraction crystallized by the next day. The solid benzylparaconic ester crystallized from warm ether as large crystals and had a m.p. of 45.5-46°. The solid ester is soluble in ether, chloroform, and alcohol, and very slightly soluble in petroleum ether.

0.0971 g substance: 0.2403 g CO_2; 0.0568 g H_2O. Found %: C 67.49; H 6.49. $C_{14}H_{16}O_4$. Computed %: C 67.72; H 6.50.

Racemic α-benzylparaconic acids. 5.1 g of the liquid ester was boiled for 4 hours with 10% hydrochloric acid. Then the alcohol and the water were distilled in vacuum. This yielded 4.49 g of an acid. The acid was crystallized from a mixture of ether and petroleum ether as thin platelets and had a m.p. of 102-103°. The acid is freely soluble in ether and alcohol, slightly soluble in water and benzene, and very slightly soluble in petroleum ether.

0.1034 g substance: 0.2475 g CO_2; 0.0534 g H_2O.
Found %: C 65.28; H 5.73. $C_{12}H_{12}O_4$. Computed %: C 65.44; H 5.49.

Saponification of the solid ester yielded an acid that fused at 134.5-135° after double recrystallization from water. It crystallized as elongated needles from a mixture of ether and petroleum ether. The acid is freely soluble in alcohol, slightly soluble in benzene, and very slightly soluble in petroleum ether.

0.1010 g substance: 0.2418 g CO_2; 0.0496 g H_2O.
Found %: C 65.28; H 5.45. $C_{12}H_{12}O_4$. Computed %: C 65.44; H 5.49.

When the acid produced from the solid ester was heated to 180-200° for 6 hours its melting point changed. It fused at 99.5-100.5° after recrystallization from a mixture of ether and petroleum ether.

A test sample, mixed with the acid prepared from the liquid ester, exhibited

no depression of the melting point, whereas it did exhibit a depression (m.p. 89-91°) when mixed with the original acid (m.p. 134.5-135°). Hence, the acid prepared from the solid ester is unstable, being transformed by heat into the stable acid recovered from the liquid benzylparaconic ester.

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THE ACTION OF AROMATIC DIAZO COMPOUNDS OF THE ALKYLACETOACETIC ESTER TYPE AS A METHOD OF SYNTHESIZING ARYL HYDRAZONES OF α KETO ACIDS, α AMINO ACIDS, AND INDOLE DERIVATIVES

XI. THE REACTION OF ETHYL CAMPHORCARBOXYLATE-3 WITH DIAZOBENZENE

V. V. Feofilaktov

The azo couplings of esters of the cyclic β-keto acids, especially cyclohexanonecarboxylic-2 acid and cyclopentanonecarboxylic-2 acid, have been studied in considerable detail and are the basis for the preparation of some indole derivatives. Such homologs of heteroauxin as γ-(indolyl-3)-γ-butyric acid [1] and β-(indolyl-3)-propionic acid [2], have been synthesized; they are of considerable interest as growth-stimulating substances that are more powerful than heteroauxin itself as root-forming factors in accelerating the vegetative propagation of various agricultural plants by grafting.

The azo coupling of these esters depends upon the nature of the cyclic ketone ester and diazo compound and upon the coupling conditions; it is either arrested at the stage of cyclic azo esters or, as the result of their "acid cleavage" and the rearrangement of the azo form into the hydrazo form, yields aryl hydrazones of an acid ester of an α-keto acid at once. Thus, in an alkaline medium, ethyl cyclopentanonecarboxylate at once forms aryl hydrazones of the acid ester of α-oxoadipic acid, as Manske and Robinson had shown [3]. In acetic acid, the coupling results in the formation of azo esters, which are, moreover, highly unstable, as Kalb and his associates, Manske and Robinson, Linstead and Wang, and the present author have shown [4].

In the case of ethyl cyclohexanonecarboxylate, azo coupling even in acetic* acid results in the direct formation of aryl hydrazone of oxopimelic acid, as Jackson, Manske and our researches have shown [1], and as Lions and Spruson have shown for an alkaline medium.

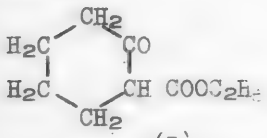
Thus, there is a certain difference in the ease with which the ring is ruptured in this reaction, a difference that depends upon the nature of the ring, viz: in the case of the ethyl ester of cyclopentanonecarboxylic acid, cyclic azo esters are relatively stable as compared to those of cyclohexanonecarboxylic acid.

We were interested in learning the behavior of ethyl camphocarboxylate (IV) under these conditions, as a bicyclic analog of both of the esters mentioned above (of cyclopentanone- and cyclohexanonecarboxylic acids), since the sparse references in the literature on this question indicate that the highly stable bicyclic system of camphor does not suffer ring rupture even in an azo coupling reaction,

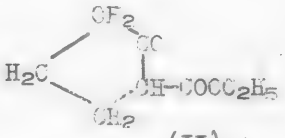
*As Linstead and Wang have shown [4] only coupling with p-nitrodiazobenzene yields a stable azo ester in acetic acid.

the reaction products being stable azo compounds.

Although the real bicyclic analog of the esters of these two β-keto acids – cyclohexanonecarboxylic (I) and cyclopentanonecarboxylic (II) acids – is ethyl norcamphocarboxylate (III) we chose the ethyl ester of camphocarboxylic acid (IV), nevertheless, for our preliminary investigation, because we intended to use its expected phenylhydrazone for the synthesis of several derivatives of homocamphoric acid.



(I)



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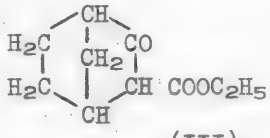
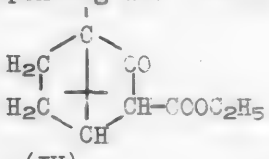
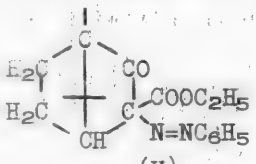


(III)

Haller [6] reacted phenyldiazonium chloride with this ester (IV) in the presence of sodium ethoxide and secured the azo ester (V). Minguin [7] reacted the nitrile (VI) with phenyldiazonium chloride and ortho and para tolyldiazonium chlorides in an alcoholic solution of potassium hydroxide and also obtained the corresponding azo nitriles (VII):



(IV)



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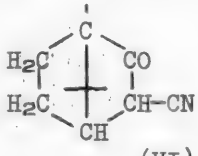
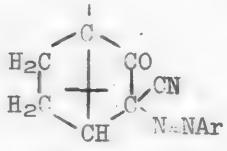
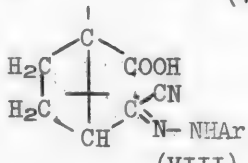


(VI)



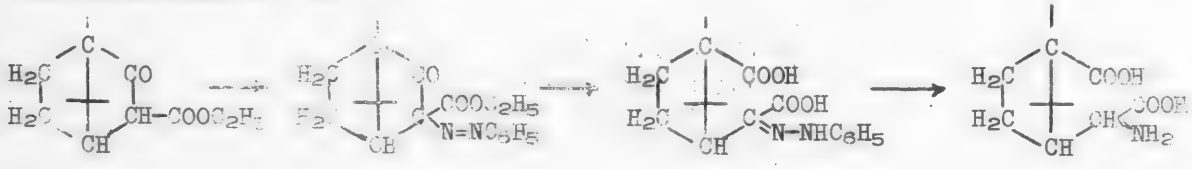
(VII)



(VIII)

It follows from these observations, as well as from the results of the present investigation, that the camphor bicyclic system is more stable than its simplest analogs, and that its azo derivatives do not suffer spontaneous rupture of the ring either during azo coupling or afterward. The expected phenylhydrazone of α-oxohomocamphoric acid can be secured only by a rather vigorous treatment of the azo ester with an alkali solution; this agrees with what Minguin found for the conversion of the azo nitriles (VII) into arylhydrazones of a seminitrile of α-oxohomocamphoric acid (VIII).

We have effected transformations according to the diagram set forth below, preparing and identifying two derivatives that apparently have not been described in the literature, viz., the phenylhydrazone of α-oxohomocamphoric acid (IX) and α-aminohomocamphoric acid (X).



(IV) (V) (IX) (X)

EXPERIMENTAL

The initial ethyl ester of camphocarboxylic-3 acid (IV), prepared by the Bruhl method [8] from natural d-camphor, had the following constants: b.p. 162-163° at 18 mm; d_4^{13} 1.0646; n_D^{13} 1.4767; MR_D 59.46; computed for the keto form – 59.50; for the enol form – 60.55 (without exaltation).

Preparation of the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid (V). The following two solutions: a) phenyldiazonium chloride, prepared from 1.3 g of aniline hydrochloride (0.01 mol), 0.70 g of sodium nitrite (0.01 mol), and 1 ml of hydrochloric acid (sp. gr. 1.19), and chilled to 0°; and b) an alcoholic solution of a sodium derivative of the ethyl camphocarboxylate, were simultaneously ad added drop by drop, with vigorous stirring, to a glass beaker fitted with a mechanical stirrer, chilled externally with ice water, and containing 2 g of crystalline sodium acetate dissolved in 4 ml of water. The solution of the sodium derivative of camphocarboxylic acid was prepared by adding 2.24 g of ethyl camphocarboxylate (0.01 mol) to an alcoholic solution of sodium ethylate, prepared by dissolving 0.23 g of sodium in 12-15 g of absolute alcohol; the reaction mixture was kept at room temperature for an hour as the ester was added to the ethylate solution.

As soon as the first few drops of these solutions were added to the beaker containing the sodium acetate, its contents turned yellow; as more drops of these solutions were added, with the stirring operating continuously, a yellow emulsion was formed, which yielded light-yellow crystals of the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid after 1 to $1\frac{1}{4}$ hours had elapsed, and the liquid became transparent.

With the reaction vessel well chilled externally and the stirrer operating at high speed, the reaction was completed within 1.5 hours (β-naphthol test); the crystals were suction filtered, washed with water and dried in an exsiccator. They weighhed 2.9 g, or 88.3% of the theoretical. Repeated experiments have proved that when the amount of ethyl camphocarboxylate used was reduced from 2.24 g to 2.0 g, keeping the amounts of the other ingredients unchanged, the yield of the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid rose to 95-96% of the theoretical (based on the ethyl camphocarboxylate).

The product consisted of canary-yellow rhombic crystals or flat tetrahedral pyramids after crystallization from petroleum ether of ligroin, which fused at 61-62° and exhibited a marked Bulow reaction (concentrated H_2SO_4 + $K_2Cr_2O_7$) – a reddish-purple color that rapidly disappeared.

> 4.079 mg substance: 10.416 mg CO_2; 2.703 mg H_2O. 3.069 mg substance: 7.822 mg CO_2; 2.032 mg H_2O. 4.460 mg substance: 0.363 ml N_2 (25°, 735 mm). 5.324 mg substance: 0.429 ml N_2 (23°, 736 mm). Found %: C 69.64, 69.51; H 7.42, 7.41; N 9.02, 9.00. $C_{19}H_{24}O_3N_2$. Computed %: C 69.47; H 7.37; N 8.53.

Thus, the compound is the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid described by Haller, though it has a slightly lower m.p. of 61-62°, as against the 65.5° given by Haller.

The latter author synthesized this compound by reacting phenyldiazonium chloride with an alcoholic solution of theester (IV) and sodium ethylate; the au author did not specify the yield.

Action of an alcoholic alkali upon the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid. Preparation of the phenylhydrazone of α-oxohomocamphoric acid (IX). 3 g of the ethyl ester of 3-benzeneazocamphocarboxylic-3 acid was heated with a reflux condenser over a water bath together with a water-alcohol solution of caustic potash (1.5 g of KOH, 2 ml of water, and 10 ml of alcohol). After 6 hours had elapsed, water was gradually added a little at a time to the solution,

which had turned orange, and heating was continued over a screen, with the condenser removed, until the alcohol had been driven off. After the aqueous alkaline solution had cooled, the slight cloudiness was filtered out, and the solution was extracted several times with ether. The traces of ether were removed by gentle heating and blowing air through the solution; then the aqueous solution was again cooled down and acidulated with hydrochloric acid. This precipitated fine pale-brown crystals of the phenylhydrazone of α-oxohomocamphoric acid (IX), which were suction filtered, washed with water, and dried; they then fused at 160-161° and weighed 2.6 g, i.e., the yield was 89.6% of the theoretical. The substance is insoluble in water or petroleum ether, and readily soluble in alcohol, acetone, acetic acid, and ether. It was recrystallized from a mixture of acetone and water by quickly chilling a filtered hot solution while stirring it, as this is the only way in which the substance can be secured in a clearly crystalline form. After repeated recrystallization, the phenylhydrazone consisted of minute acicular crystals with a pale-brown tint, which fused at 165-166.5° with decomposition. An alcoholic solution exhibits an acid reaction, and the solution turns a quickly disappearing purple with concentrated sulfuric acid and potassium dichromate (Bulow reaction). We were unable to discover any dimorphism.

2.912 mg substance: 6.875 mg CO_2; 1.850 mg H_2O. 4.601 mg substance: 10.832 mg CO_2; 2.834 mg H_2O. 3.21 mg substance: 0.257 ml N_2 (22°, 748 mm). 3.00 mg substance: 0.238 ml N_2 (22°, 748 mm). Found %: C 64.38, 64.21; H 7.04, 6.89; N 9.12, 9.04. $C_{17}H_{22}O_4N_2$. Computed %: C 64.11; H 6.97; N 8.80.

Titration. 12.40 mg substance (in 10 ml of alcohol, phenolphthalein) combined with 7.85 ml of 0.01 N NaOH. 11.75 mg (in 10 ml of alcohol, phenolphthalein) combined with 7.33 ml of 0.01 N NaOH. Equivalent: 158.0, 160.3. $C_{17}H_{22}O_4N_2$. Computed 159.1, (dicarboxylic acid).

Reduction of the phenylhydrazone of α-oxohomocamphoric acid. Preparation of α-aminohomocamphoric acid (X). 1.5 g of the unrecrystallized phenylhydrazone (with a m.p. of 160-161°) was dissolved in 25 ml of ethyl alcohol, 1.5 g of zinc dust was added a little at a time, together with drops of an alcoholic solution of hydrogen chloride from time to time, to the solution, which was chilled externally. Reduction was complete 6 hours later (negative Bulow reaction). The excess zinc dust was filtered out, the alcohol was driven off, the residue was dissolved in water, the chlorine ion was removed by agitating the solution with freshly precipitated silver carbonate, and the metals were precipitated with hydrogen sulfide and filtered out. The filtrate was concentrated in vacuum, yielding a colorless crystalline deposit of α-aminohomocamphoric acid, which weighed 0.97 g after standing in an exsiccator, the yield of the crude product thus being 89.8% of the theoretical. The α-aminohomocamphoric acid was recrystallized from hot water (with animal charcoal), after which it consisted of lustrous, colorless, minute needles, with a m.p. of 185° (in a sealed capillary). Its aqueous solution is turned an intense blue by boiling it for a short time with cupric oxide.

3.428 mg substance: 7.210 mg CO_2; 2.521 mg H_2O. 3.600 mg substance: 7.560 mg CO_2; 2.654 mg H_2O. 3.31 mg substance: 0.174 ml N_2 (23°, 746 mm). 3.06 mg substance: 0.166 ml N_2 (23°, 746 mm). Found %: C 57.36, 57.27; H 8.23, 8.24; N 5.95, 6.00. $C_{11}H_{19}O_4N$. Computed %: C 57.60; H 8.35; N 6.11.

SUMMARY

The bicyclic camphor system is more stable than the corresponding monocyclic systems – the esters of cyclohexanone- and cyclopentanonecarboxylic acids; the azo coupling of the ethyl ester of camphocarboxylic-3 acid produces a stable azo ester,

the possible rupture of the ring between the second and third carbon atoms of camphor not taking place.

When such azo esters are hydrolyzed by an alkali solution, however, the bicyclic camphor system is ruptured between the second and third carbon atoms, yielding the phenylhydrazone of α-oxohomocamphoric acid. We were unable to detect any dimorphism of the phenylhydrazone.

Reducing this phenylhydrazone produces a high yield of α-aminohomocamphoric acid; this is a convenient method of preparing the latter.

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ANHYDRIDES, AMINO AND GUANIDO DERIVATIVES OF CARBOHYDRATES AND POLYHYDRIC ALCOHOLS

I. 6-AMINO, 6-METHYLAMINO, AND 6-GUANIDO DERIVATIVES OF GLUCOFURANOSE

S. N. Danilov and I. S. Lishansky

The wide distribution of chitosamine in natural substances (chitinmucoitinsulfuric and hyaluric acids, heparin, etc.), as well as the recently discovered data on the entry of N-methyl-l-glucosamine and a diguanido derivative of mesoinositol into the streptomycin molecule and other reports indicate that the ammonium derivatives of the carbohydrates and polyhydric alcohols are an important class of substances, on which little research has been done. The anhydride forms of the sugars and the polyhydric alcohols are highly interesting because of their importance in various syntheses, including those occurring in nature, which are also particularly valuable for the preparation of various nitrogenous derivatives. It should be stressed that the addition of amines, especially methylamine, to α-oxides was first investigated by N.D.Zelinsky [1]. Somewhat later K.A.Krasusky [2] made a detailed study of the addition of various amines (ammonia, piperidine, and piperazine) to ethylene, isobutylene, trimethylethylene, and isopropylethylene oxides and laid down the rule that in these reactions an alcohol with a hydroxyl group is always formed at the least hydrogenated carbon atom.

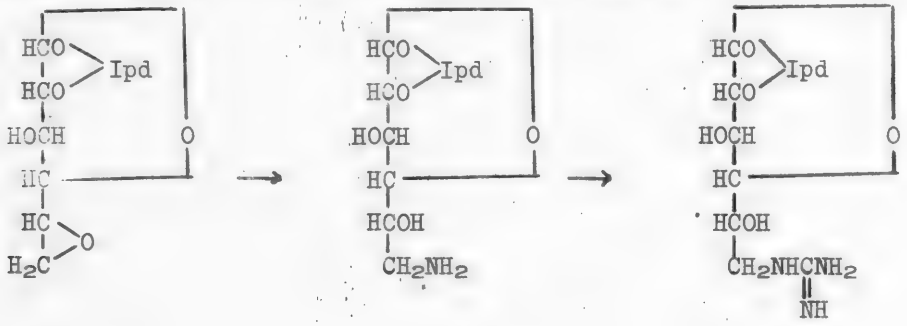
We have some information on the amino and methylamino derivatives of the monoses, together with suggestions for their synthesis (via the cyanhydrins, halogen derivatives, tosyl esters, and the anhydrides of the monoses) [3], the typical amines being those of monoses and ammonia that contain an ammonia group replacing the hydroxyls of the alcohol groups instead of being attached to the carbonyl carbon atom. In general, there is not enough information on the guanido derivatives of the sugars; the only information we have is on the guanido compounds formed with the participation of the carbonyl group [4].

It is asserted [4] that reacting alcoholic solutions of carbohydrates with guanidine results in the formation of finely crystalline, extremely hygroscopic, rather unstable substances that are insoluble in organic solvents and about which, to tell the truth, we know very little.

In our researches we have effected the synthesis of a guanido derivative of a monose, with a guanido group replacing the alcoholic hydroxyl group, as well as its corresponding amino and methylamino derivatives. We used an anhydride of glucose, viz.: (1,2)-isopropylidene-(5,6)-anhydroglucofuranose (I), produced as follows, in accordance with the specifications in the literature: glucose → (1,2)(5,6)-diisopropylideneglucofuranose → (1,2)-isopropylideneglucofuranose → (1,2)-isopropylidene-6-tosylglucofuranose → (1,2)-isopropylidene-(5,6)-anhydroglucofuranose.

We have made substantial improvements in this series of reactions, involving carrying it out in separate stages (syntheses of the diacetone and, especially, the monoacetone derivatives of glucofuranose, and the recovery of the 6-tosyl ester of the latter). This acetonated anhydride has been reacted with ammonia and methylamine by other authors [4], but they do not specify the experimental conditions; they described the amino and methylamino derivatives as syrups. The structure of these derivatives is that of 6-desoxy-6-aminoglucofuranose (and 6-methylamino-, respectively). We have isolated both of these compounds as powders with a strong alkaline reaction and have identified them as crystalline carbonates.

We synthesized the corresponding 6-guanidomonoacetoneglucoses (III) from the above-mentioned 6-desoxy-6-aminomonoacetoneglucose (II). Reacting this amine with the hydroiodide of S-methylisothiourea as well as with the base O-methylisourea (V) yielded the guanido derivative (III), which was strongly alkaline and produced a raspberry-red color in the Sakaguchi reaction [5] (a few drops of a 0.1% solution of α-naphthol, a 0.5% solution of caustic soda, and 1-2 drops of a 1% solution of sodium hypochlorite to a solution of a guanido derivative).

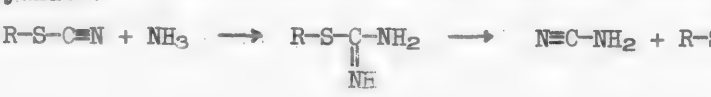


(I) (II) (III)

The hydriodide of (1,2)-isopropylidene-6-desoxy-6-guanidoglucose was prepared as a hygroscopic yellowish powder. The salt was converted into a free base by treating it with silver oxide in acetone; its m.p. was 110-115°, and its composition was $C_{10}H_{18}O_5N_3$. The base was strongly alkaline in an aqueous solution and formed a picrate in the shape of tiny yellow crystals, with a m.p. of 148-149°. The tribenzene derivative, $C_{31}H_{31}O_8N_3$, m.p. 88-90°, contained two benzene groups attached to carbon atoms (acylated alcoholic hydroxyls) and one attached to a nitrogen atom (acylated guanido group). The tribenzoate did not exhibit the Sakaguchi reaction, like the well-known acyl derivative of guanidine. An endeavor to prepare the guanido derivative by reacting (1,2)-isopropylidene-(5,6)-anhydroglucofuranose with an alcoholic guanidine solution was unsuccessful.

Let us pause for a moment to consider the way in which the guanido derivatives are formed when the salt of S-methylisothiourea or the base O-methylisourea act upon the amino sugars. Interpretations of the reaction of the amino derivatives with an S-alkylisothiourea or an O-alkylisourea vary. The older view was that the alkylisourea is first added to the amine, after which the resulting coordination compound breaks down, yielding the guanido derivative and a mercaptan (or an alcohol, in the case of an O-alkylisourea) [6,7].

The well-known references in the literature [8,9] to the decomposition of S-methylisothiourea in two ways, into: a) cyanamide and a mercaptan, and b) ammonia and methyl thiocyanate:



however, led to the highly probable conclusion that the guanidizing action of S-methylisothiourea is due to its decomposition, resulting in the formation of cyanamide, which then combines with the amine [10].

This interpretation of the reaction is confirmed by the familiar reaction between amines and previously prepared cyanamide, which results in the formation of guanido derivatives, although extremely slowly.

It might be thought that the guanidizing action of O-methylisourea can likewise be explained by its breakdown in two ways, cyanamide being formed in one of them:

$$CH_3OCN + NH_3 \longleftarrow CH_3O-\underset{\underset{NH}{\|}}{C}-NH_2 \longrightarrow N\equiv C-NH_2 + CH_3OH.$$

The existence of such a decomposition of O-methylisourea is mentioned in the literature, but no importance was attached to it.

The varying ability of the amines to react with S-methylisothiourea and O-methylisourea leads us to believe that the amino derivative must be rather strongly basic for this reaction to occur; this is the case in 6-aminoacetoneglucose.

$$R-NH_2 + N\equiv C-NH_2 \longrightarrow R-NH-\underset{\underset{NH}{\|}}{C}-NH_2$$

EXPERIMENTAL

Diacetone- and Monoacetoneglucofuranoses

The initial substance for the synthesis of the amino derivatives – (1,2)-isopropylidene-(5,6)-anhydroglucofuranose – was prepared from the corresponding 6-tosyl derivative by reacting the latter with a methoxide. Though this reaction plan is well known [11], we have made several improvements in it during our experiments, so that we shall have to describe our experiments briefly.

The di- and monoacetone derivatives of glucose have been known for a long time, but the preparation of these products with high and unvarying yields meets with difficulty. In preparing the diacetone derivative it is preferable to substitute stirring with a propeller stirrer (approx. 1400 rpm) for shaking the glucose together with acetone in a mechanical agitator, in order to speed up the dissolution of the glucose and, most important, to neutralize the sulfuric acid used as a catalyst as rapidly and fully as possible (glucose - acetone ratio = 1:20; sulfuric acid = 5% of the acetone by weight; time = 4-5 hours). The reaction constituents must be completely anhydrous, and the hydrolyzing action of the water evolved in the condensation of the glucose with the acetone and in the neutralization of the sulfuric acid must be prevented by the use of soda (240 g of anhydrous soda to 100 g of acid; neutralization time: from 2 to 5 hours). It is advisable to continue this mixing with soda for a long time, and then to set the mixture aside for 12-24 hours for the binding of the resulting water by the sodium sulfate to be complete and for the salt to crystallize out. The decolorized acetone solution, from which the salt has been filtered out, was evaporated – at first over a water bath at atmospheric pressure, and toward the end in vacuum to drive off the traces of acetone and its condensation products. The thick, dark-yellow syrup left within the flask was dissolved in sulfuric ether, and the solution was set aside to stand overnight in ice. The crystalline mass that formed was suction filtered in a funnel, pulverized, washed with cold petroleum ether (b.p. 60-80°), again suction filtered, and recrystallized from boiling petroleum ether. The substance (diacetoneglucofuranose) was obtained as elongated snow-white needles, which had a m.p. of 111-112° after drying in vacuum above paraffin. The yield of diacetoneglucosefuranose was 65% of the calculated value.

There are statements in the literature [12] to the effect that acetone

condenses readily with glucose without undergoing distillation, and that acetone used once in this reaction can be reactivated by adding 0.5% acetaldehyde to it. Our experiments have shown that distilling acetone twice above calcined potash does not interfere with its condensation with glucose. Re-using the acetone after desiccating it, however, results in a weakening of its reactivity, a longer time being required for the reaction. Adding 0.5% of acetaldehyde to the spent acetone accelerates the reaction considerably, the solution growing much darker, but the reaction product is harder to crystallize, probably owing to part of the glucose reacting with the acetaldehyde.

Various methods have been recommended for converting a diacetone derivative into a monoacetone one [11,13]. The best results are obtained with hydrolysis by nitric acid in a heated ethyl acetate solution (Hickson method), which is only sketchily described in the literature.

The diacetoneglucose was dissolved in the cold in 8 times its weight of ethyl acetate, nitric acid (sp. gr. 1.13) was added on the basis of 1 ml of acid to 100 ml of solution, and the mixture was placed in a hot water bath. In our experiments heating was done at such a rate that the ethyl acetate started boiling within 3 minutes, after which the heating was continued for another 2 minutes. The yield of monoacetoneglucose was about 70% of the theoretical; its m.p. was 161-162°.

Hydrolyzing the diacetoneglucose in a 50% aqueous solution of methanol with sulfuric acid at room temperature (Reichstein method) is more laborious, though it produces a fairly good yield (65%).

The method involving the single-stage synthesis of (1,2)-isopropylideneglucofuranose by using boric acid (the Vargha method) does not produce high yields. Condensing the glucose with acetone proceeds smoothly in the presence of sulfuric acid: the solution hardly darkens, but the stage in which the boric acid is split off by the methanol also involves the partial hydrolysis of the monoacetone compound, which lowers the product yield and contaminates it.

(1,2)-Isopropylidene-6-tosylglucofuranose.

The tosyl derivative was prepared by reacting 1 mol of p-toluene sulfochloride with the monoacetone glucose. In our experiments this synthesis has been improved over the existing specifications [11] in respect to the recovery of the tosyl ester. After esterification in a mixture of chloroform and pyridine, the latter is not driven off, but washed out of the chloroform solution with water. The desiccated chloroform solution was evaporated in vacuum at a temperature not over 40° and crystallized by chilling with ice. This treatment takes the place of the prolonged extraction with ether after the pyridine and chloroform have been driven off, proposed in the above-mentioned specifications. The resultant yield of the tosyl ester was about 55%, as a white powder with a m.p. of 106-107°. The substance slowly turned into a black, tarry mass when kept for a long time (over 2 months).

(1,2)-Isopropylidine-(5,6)-anhydroglucofuranose.

The glucose anhydride was prepared from the tosyl ester described above, but we were unable to raise the yield above 55%, though a yield of as high as 80% is given in the literature [3d], which is hard to achieve, possibly because of the anhydride's high sensitivity to alkali. A solution of (1,2)-isopropylidene-6-tosylglucofuranose in anhydrous chloroform was rapidly chilled to -20°. As soon as the first crystals appeared on the bottom of the bottle, a freshly prepared solution of sodium methoxide in anhydrous methanol (1 mol), chilled to -15°, was poured through a small funnel. Then the bottle was closed with a glass stopper and vigorously shaken by hand until a transparent gel was formed, after which it was

left in the freezing mixture for another 25 minutes. Cold water was added, the bottle was shaken until the gel was broken up, the chloroform layer was removed as rapidly as possible to avoid cleavage of the anhydride, and the aqueous alcohol layer was extracted with cold chloroform. The chloroform solution was passed through a dry filter and desiccated with sodium sulfate. The chlorofrom was driven off in vacuum, and the residue was recrystallized from benzene. This yielded 50-55% of the anhydride, as tiny thin white needles, with a m.p. of 133-134°. The loss of anhydride is due to its high solubility in water and its rapid hydrolysis in an alkaline medium (during extraction from the water-alcohol solution).

Action of Ammonia upon (1,2)-Isopropylidene-(5,6)-anhydroglucofuranose.

There is a reference in the literature to an experiment involving the action of ammonia upon this glucose anhydride, but the conditions under which the synthesis was effected are not mentioned. The amino derivative, in which the amino group is assumed to be attached to the sixth carbon atom, was prepared only as a syrup [3d]. We synthesized the amino derivative by reacting the anhydride with an 8% solution of anhydrous ammonia in anhydrous methanol. The resulting solution was kept at 20° for 3 hours, after which it was evaporated in vacuum to a thick syrup and subjected to evacuation at 80° for 2 hours in order to remove any traces of ammonia. The resulting syrup did not crystallize when chilled or when kept in the exsiccator for a long time over caustic potash. The product did solidify, however, when kept for a long time in vacuum (2 mm) over phosphoric anhydride. This yielded a powder (after grinding in an agate mortar), which was extremely hygroscopic, readily soluble in water, and strongly alkaline with phenolphthalein. The yield was 95% of the theoretical; the m.p. was 60-65° (in a sealed capillary).

The amine was purified by converting it into a carbonate. An alcoholic solution of the base was saturated with carbon dioxide and evaporated in vacuum at 20°. The residue was recrystallized from neutral ethyl acetate. The substance had a m.p. of 90-95° after having been desiccated in vacuum above phosphoric anhydride.

0.1227 g substance: 6.1 ml N_2 (764 mm, 21°). 0.1610 g substance: 8.15 ml N_2 (763 mm, 21°). Found %: N 5.76, 5.83. $(C_9H_{17}O_5N)_2H_2CO_3$. Computed %: N 5.59.

The synthesized mass may be assumed to be (1,2-isopropylidene-(5,6)-anhydroglucofuranose.

Action of Methylamine upon (1,2)-Isopropylidene-(5,6)-anhydroglucofuranose.

The methylamine was prepared in the usual manner, as a hydrochloride, by heating a 38% aqueous solution of formaldehyde with ammonium chloride. The product was purified by recrystallizing it from absolute alcohol and then from n-butyl alcohol, in which ammonium chloride is wholly insoluble. The pure base was recovered by pouring the methylamine hydrochloride, dissolved in as little anhydrous methanol as possible, into a hot solution of sodium methylate in methanol. The resulting free methylamine was absorbed in absolute methanol at room temperature.

The reference in the literature to the synthesis of the methylamino derivative does not contain a description of the experiment, the amine having been produced as a syrup [3d].

We prepared this derivative by using the solution of methylamine in absolute methanol to introduce amino groups. The resultant syrupy substance was converted into a carbonate by saturating the alcoholic solution with carbon dioxide. The carbonate was secured as a colorless, finely crystalline powder with a m.p. of 131-134°.

0.1378 g substance: 6.5 ml N_2 (761 mm, 22°). 0.1502 g substance: 7.15 ml N_2 (760.5 mm, 23°). Found %: N 5.42, 5.44. Computed for $(C_{10}H_{19}O_5N)_2 \cdot H_2CO_3$ %: N 5.29.

Inasmuch as the references in the literature do not clearly indicate the way in which guanido derivatives of the carbohydrates are produced, we ran experiments of various sorts to find a way of introducing the guanido group into the monose molecule. Various efforts to react (1,2)-isopropylidene-(5,6)-anhydroglucofuranose with guanidine itself, both in aqueous solution (60°, 8 hours) and in alcoholic solution (20°, 3 days, or 80°, 2 hours) failed to produce guanido derivatives. We secured neutral products containing no nitrogen, the formation of which was accompanied by the partial rupture of the anhydride ring and by methylation.

Action of S-Methylisothiourea and O-Methylisourea upon (1,2)-Isopropylidene-(5,6)-anhydroglucofuranose.

We wish to point out that we have improved the usual method employed for preparing S-methylisothiourea, which customarily involves keeping a mixture of crystalline thiourea and a large quantity of methyl iodide (as much as 500% of the calculated quantity) for several days at room temperature and yields a product contaminated with thiourea.

We have developed the following synthesis procedure. 20 g of finely pulverized thiourea was heated to 35-40° with 20 ml of absolute methanol in a 100-ml flask fitted with a ground-glass condenser, and 40 g (1.08 mols) of methyl iodide was added drop by drop, which caused the thiourea to dissolve gradually. After the methyl iodide was added, the flask was kept at 40° for another half hour, and then the solution was transferred to a crystallizing pan. Large crystals of S-methylisothiourea hydriodide formed within 2 hours at room temperature. The product was purified by filtering it out of the mother liquor, crushing it to a powder, and washing it with chloroform. The product was then dried in vacuum above paraffin and phosphoric anhydride and stored away from light. The m.p. of S-methylisothiourea hydriodide is 117°.

The S-methylisothiourea hydroiodide was added a little at a time to 0.01 mol of the original amine dissolved in 50 times its weight of water, the temperature of the reaction mixture being kept at 80°. 0.01 mol of S-methylisothiourea was added during the course of six days. The solution was then evaporated in vacuum, and the remaining syrup was dissolved in absolute methanol and precipitated with sulfuric ether. The colorless oil that settled out was kept in an exsiccator above sulfuric acid for 2 weeks until it turned into a hyaline mass (totalling 150% by weight of the initial amine).

Part of the product was converted into a benzoyl derivative by treating it with three times its weight of benzoyl chloride in pyridine solution. The mixture evolved heat and turned dark red because of the liberation of iodine. The solution was kept at 20° for 4 days, after which it was diluted with dichloroethane and washed with water, 3% hydrochloric acid, sodium thiosulfate and bicarbonate solutions, and again with water. The solution was then desiccated with sodium sulfate, and the dichlorethane driven off in vacuum; the resulting syrup was kept for several weeks in an exsiccator above sulfuric acid, after which time the substance crystallized. The crystals were suction-filtered on a glass filter, washed with chilled acetone, and recrystallized from a small quantity of the latter.

The substance had a m.p. of 88-90° after being desiccated above phosphoric anhydride. A water-acetone solution of the substance showed no coloration when tested for the guanido group. Analysis of the substance indicated it was the tribenzoate of a guanido derivative of monoisopropylideneglucose (one acyl group attached to nitrogen, and two attached to C_3 and C_5.

0.1736 g substance: 11.5 ml N_2 (752 mm, 19°). Found %: N 7.59.
$C_{31}H_{31}O_8N_3$. Computed %: N 7.33.

The absence of any coloration when tested with the reagent for the guanido

group agrees with the statements in the literature concerning the negative (Sakaguichi) reaction in acylated guanido derivatives.

In another experiment, the synthesis took a shorter time: An aqueous solution of 4.0 g of (1,2)-isopropylidene-6-desoxy-6-aminoglucofuranose and 4.0 g of S-methylisothiourea hydriodide was heated to 80° for 4 hours. Driving off the water in vacuum yielded a tacky mass that was insoluble in benzene or chloroform, but was soluble in acetone, though it could not be crystallized. The product was dissolved in acetone, the acetone was driven off, and the residue was kept for a long time in vacuum above phosphoric anhydride. The resultant hyaline mass was pulverized to a yellowish hygroscopic powder. The free base was isolated by agitating an acetone solution with freshly prepared moist silver oxide. The filtered solution was evaporated in vacuum, and the residue was kept in vacuum above phosphoric anhydride for 10 days, then ground to a powder and again dried out. The substance has a m.p. of 110-115° (in a sealed capillary) and is extremely hygroscopic. Its solution is strongly basic and turns the reagent for the guanido group a bright raspberry-red.

0.1004 g substance: 14.3 ml N_2 (761 mm, 20°). 0.0983 g substance: 13.8 ml N_2 (763 mm, 20°). Found %: N 16.47, 16.32. Computed for $C_{10}H_{19}O_5N_3$ %: N 16.09.

The substance has the composition of a guanido derivative of monoisopropylidene glucose – (1,2)-isopropylidene-6-desoxy-6-guanidoglucofuranose (in view of the known structure of the original amine).

An alcoholic solution of picric acid was added to an alcoholic solution of the base. The yellow powder secured by evaporating the alcohol was recrystallized from aqueous alcohol. The picrate consists of minute acicular crystals, with a m.p. of 148-149°.

The same guanido derivative that was synthesized from the S-methylisothiourea is produced when the amino sugar is treated with O-methylisourea. The latter substance was prepared by triturating red mercury oxide under a layer of sulfuric ether with finely pulverized thiourea, the whole being constantly chilled with ice. The black, pasty precipitate of mercury salts was washed several times with ether. After the ether had been driven off, the syrupy residue turned into a crystalline mass of cyanamide when deeply chilled. After it had been desiccated in vacuum above phosphoric anhydride, the dry cyanamide was dissolved in anhydrous methanol containing an equivalent quantity of hydrogen chloride, and then set aside to stand overnight at room temperature. The solution was evaporated to half its volume in vacuum and then chilled with ice water. The precipitated acicular crystals of O-methylisourea hydrochloride were suction filtered and desiccated in vacuum above phosphoric anhydride. The free base was secured by adding a chilled solution of a calculated quantity of sodium methoxide to a solution of the salt in absolute methanol, the precipitated sodium chloride being filtered out after the mixture had been kept at 0° for 30 minutes.

Experiments were made on the reaction of (1,2)-isopropylidene-6-desoxy-6-aminoglucose with O-methylisourea and with the free base. An experiment with a solution of the salt in absolute methanol at 20° for 8 days failed to produce the guanido derivative. But when a freshly prepared solution of the O-methylisourea base was added to a solution of guanidoglucose in 25 times its weight of absolute methanol, and the mixture was kept at room temperature for 3 days, driving off the alcohol left a residue containing the guanido derivative, which turned the guanido-group reagent a bright raspberry-red. The substance readily formed a picrate with a m.p. of 148°, which exhibited no depression of the melting point when mixed with the picrate of the previously prepared sample of guanidoglucose (using the salt of S-methylisothiourea).

Inasmuch as the preparation of S-methylisothiourea is simpler than that of

O-methylisourea, the former method should be preferred. To prevent the mercaptan evolved during the reaction from causing trouble, reliable absorbing equipment must be used, best of all being activated charcoal impregnated with copper monochloride and dried at 200°. In this absorbent the mercaptan is quantitatively oxidized to a sulfo acid.

SUMMARY

1. The methods of preparing some sugar derivatives (acetone derivatives of glucose and 6-tosylmonoacetoneglucoses) have been perfected.

2. The following have been identified as their carbonates: (1,2)-isopropylidene-6-desoxy-6-aminoglucofuranose and (1,2)-isopropylidene-6-desoxy-6-methylaminoglucofuranose.

3. It has been established that the method of synthesizing guanido derivatives by reacting an amine with S-methylisothiourea and with O-methylisourea is applicable to the sugars, the 6-amino derivative of glucose having yielded (1,2)-isopropylidene-6-desoxy-6-guanidoglucofuranose, as its hydriodide, the free base, and its picrate.

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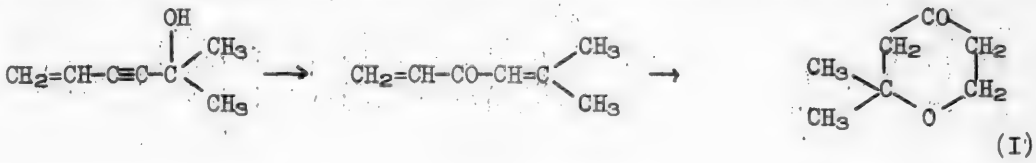
DERIVATIVES OF ACETYLENE

125. SYNTHESES BASED ON DIVINYLACETYLENE.

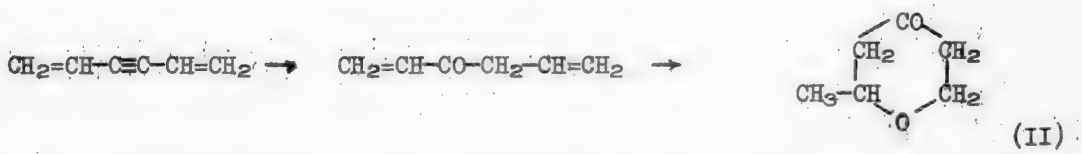
TRANSFORMATIONS OF 2-METHYL-4-VINYLETHYNYL-4-PYRANOL

I. N. Nazarov and S. A. Vartanyan

Simple methods have been developed in our laboratory for the preparation of diverse tetrahydro-γ-pyrones by isomerizing vinylethynylcarbinols [1], as well as by hydrating some divinylacetylenic hydrocarbons [2]. Of these reactions, special interest attaches to the conversion of commerical dimethylvinylethynylcarbinol intp 2,2-dimethyltetrahydro-4-pyrone (I) [3] and of divinylacetylene into 2-methyltetrahydro-4-pyrone (II) [4], which makes these pyrones readily accessible products.



(I)



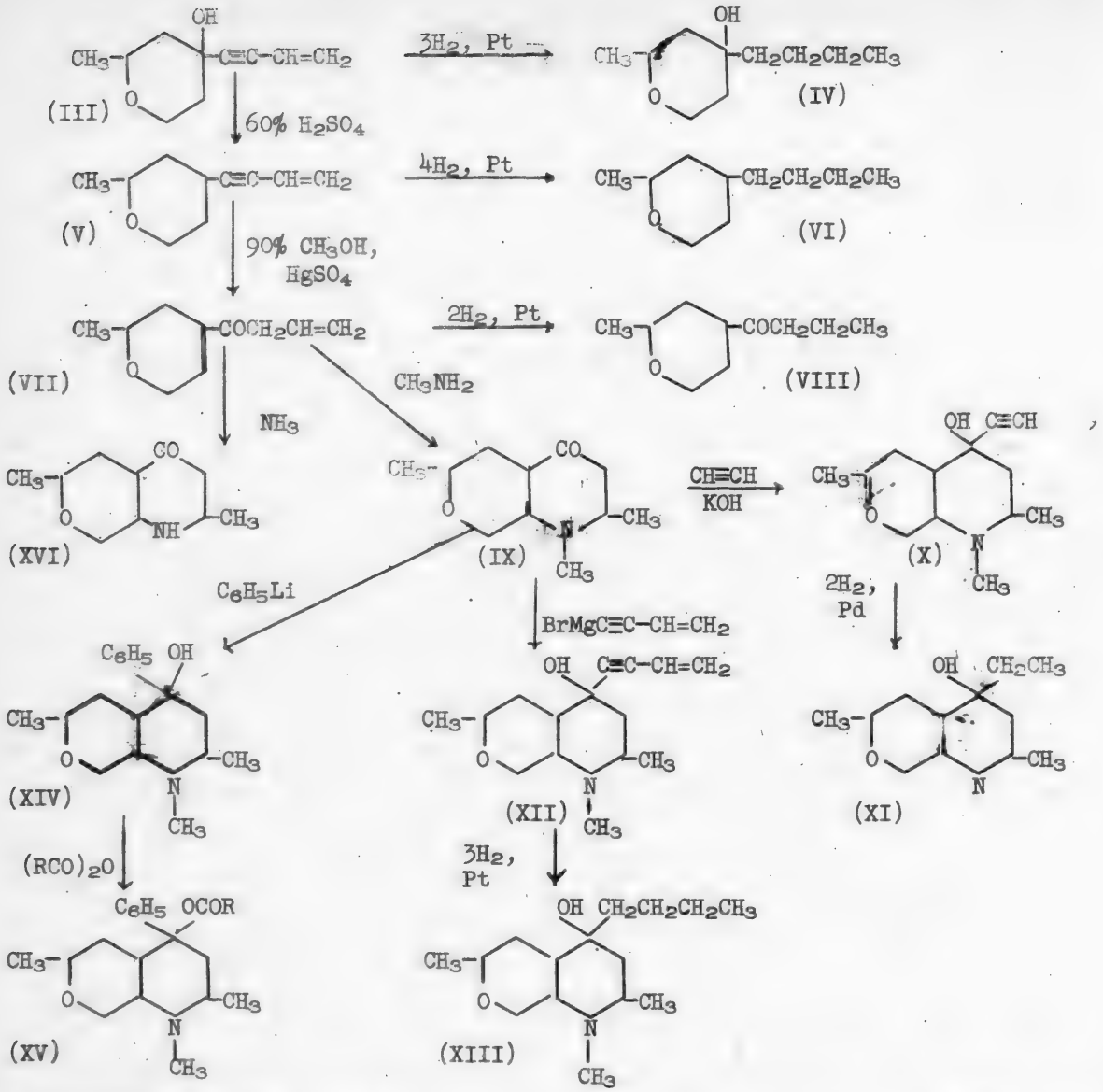
(II)

As one of the present authors pointed out in a previous report from our laboratory [5], the tetrahydro-γ-pyrones condense readily with vinylacetylene, forming the corresponding 4-vinylethynyltetrahydropyran-4-ols, which can enter into the various characteristic transformation of aliphatic and alicyclic vinylethynylcarbinols [6].

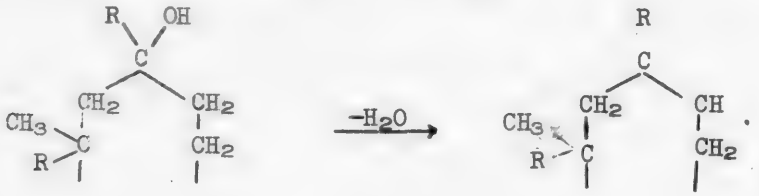
The present paper describes the transformations of 2-methyl-4-vinylethynyltetrahydropyran-4-ol (III), which was synthesized with a yield of some 80% by reacting vinylacetylenemagnesium bromide with 2-methyltetrahydro-4-pyrone (II). The vinylacetylenic pyranol (III) is easily dehydrated by 60% sulfuric acid at 65° in benzene solution, producing a 75% yield of 2-methyl-4-vinylethynyl-Δ^4-dihydropyran (V), the hydrogenation of which in an alcohol solution with a Pt catalyst results in the absorption of four molecules of hydrogen and the formation of 2-methyl-4-butyltetrahydropyran (VI).

In a similar hydrogenation, the vinylacetylenic pyranol (III) absorbs three molecules of hydrogen, yielding 2-methyl-4-butyltetrahydropyran-4-ol (IV).

Hence, the pyranol (III) is dehydrated only in one direction, giving rise to

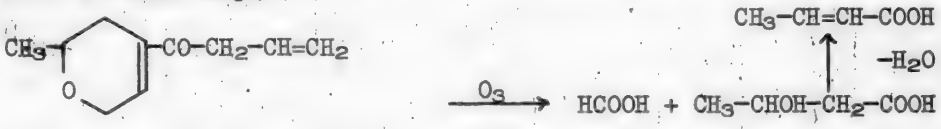


a double bond in the normal (unsubstituted) chain of carbon atoms. 2,2-Dimethyl-4-vinylethynyltetrahydropyran-4-ol [6], β-methoxyethylisobutylvinylethynylcarbinol [7], metamethylcyclohexanol [8], propylisobutylcarbinol, and n-butylisobutylcarbinol [9], in which the double bond is likewise formed in the normal (unbranched) part of the molecule, are dehydrated in the same way:



(R = H or CH_3).

When the dienyne (V) is hydrated in aqueous solutions of methanol, with mercurous sulfate present, we get a yield of some 80% of allyl-2-methyl-Δ^4-dihydro-4-pyranyl ketone (VII), its hydrogenation with a Pt catalyst resulting in the absorption of two molecules of hydrogen and the formation of propyl-2-methyl-4-tetrahydropyranyl ketone (VIII). The structure of the dienone (VII), especially the position of the double bond in the ring, was proved by ozonating it; this gave a high yield of formic and β-hydroxybutyric acids. Heating the latter with dilute sulfuric acid dehydrogenated it to crystalline crotonic acid, which exhibited no depression when mixed with a known sample:



Like the other vinyl allyl ketones, the dineone (VII) reacts readily with ammonia and primary amines [10], giving high yields of the corresponding bycyclic γ-piperidones, which contain a tetrahydropyran ring in addition to a piperidine ring. For example, when the dienone (VII) was reacted with an aqueous solution of methylamine, we secured a yield of 95% of the bicyclo pyranic γ-piperidone (IX). Powdered potassium peroxide causes the latter to condense readily with acetylene [11], yielding about 80% of the acetylenic piperidol (X), which absorbs two molecules of hydrogen when hydrogenated with a Pd catalyst, forming the bicyclo pyranic ethyl-γ-piperidol (XI). By reacting the bicyclo pyranic piperidone (IX) with vinylacetylenemagnesium bromide [12] we secured a yield of approximately 60% of the vinylacetylenic γ-piperidol (XII), which absorbs three molecules of hydrogen when hydrogenated with a Pt catalyst, being converted into butyl-γ-piperidol (XIII). The action of phenyllithium [13] upon the bicyclo pyranic piperidone (IX), yielded 70% of phenyl-γ-piperidol (XIV), the latter's esterification with acetic and propionic anhydrides yielding the respective esters (XV). We were unable to secure the benzoic ester of phenyl-γ-piperidol (XIV) by benzoylating it with benzoyl chloride, always getting the hydrochloride of the initial piperidol (XIV) instead. Treating the dienone (VII) with aqueous ammonia produces a high yield of a secondary (not substituted at the nitrogen) bicyclo pyranic γ-piperidone (XVI), which may also serve as an important starting product for the synthesis of various piperidine series. The latter are interesting in connection with the search for new physiologically active substances, especially anesthetics.

It is very likely that all the alcohols and esters described in this paper were prepared as two geometrical isomers, which cannot be separated by distillation. The hydrochlorides of these compounds fused throughout a very wide temperature range, but we were likewise unable to separate them because of their hygroscopicity and their inability to crystallize. These hydrochlorides were prepared in the usual manner: by reacting anhydrous hydrogen chloride with a solution of the base in absolute ether. They were washed by decanting them repeatedly with anhydrous ether and then desiccated in a vacuum exsiccator above phosphoric anhydride, after which they looked like amorphous powders, which deliquesced upon exposure to the air and settled out as a viscous noncrystalline mass when an endeavor was made to recrystallize them from various solvents.

EXPERIMENTAL

The initial 2-methyltetrahydro-4-pyrone (II) was prepared, as described earlier [4], by hydrating divinylacetylene; its constants were as follows: b.p. 169-170° at 750 mm; n_D^{20} 1.4440.

Synthesis of 2-methyl-4-vinylethynyltetrahydropyran-4-ol (III). Ethylmagnesium bromide was prepared in a round-bottomed flask, fitted with a mechanical stirrer, a

dropping funnel, and a reflux condenser, from 48 g of magnesium and 200 g of ethyl bromide dissolved in 700 ml of absolute alcohol. Then 160 g of gaseous vinylacetylene was passed through the ether solution of ethylmagnesium bromide, which was chilled with ice water, for 3 hours, after which the reaction mixture was stirred for 2 hours at room temperature and for 1 hour while the ether boiled until no more ethane was evolved. 175 g of 2-methyl-tetrahydro-4-pyrone dissolved in an equal volume of ether was added drop by drop in the course of 6 hours to the resulting vinylacetylenemagnesium bromide, which was chilled to -10°. Then the mixture was stirred for another 6 hours at 20° and for 1 hour at the boiling point of the ether. The product was hydrolyzed with 600 ml of 8% sulfuric acid and extracted with ether; the ether solution was neutralized with sodium bicarbonate and desiccated with sodium sulfate. Distillation of the product in vacuum resulted in the recovery of 198 g of 2-methyl-4-vinylethynyltetrahydropyran-4-ol (III) with a b.p. of 100-101.5° at 4 mm, which has been described previously [5]

n_D^{20} 1.5058; d_4^{20} 1.0252; MR_D 47.21; Computed 46.88.

3.880 mg substance: 10.264 mg CO_2; 3.100 mg H_2O. 5.660 mg substance: 14.970 mg CO_2; 4.397 mg H_2O. Found %: C 72.19, 72.18; H 8.56, 8.51. $C_{10}H_{14}O_2$. Computed %: C 72.29; H 8.43.

The vinylacetylenic pyranol (III) is a colorless liquid, as viscous as glycerol and odorless. When left to stand without a stabilizer, it turns into a jelly within 10 days, becoming a solid, transparent, slightly yellow, hyaline polymer after 27 days have elapsed. When hydrogenated with a Pt catalyst, the vinylacetylenic pyranol (III) absorbs three molecules of hydrogen, forming 2-methyl-4-butyltetrahydropyran-4-ol (IV), with a b.p. of 89-90° at 4 mm; n_D^{20} 1.4610, which has been described earlier [5].

Dehydration of 2-methyl-4-vinylethynyltetrahydropyran-4-ol. A mixture of 120 g of the vinylacetylenic pyranol (III), 120 g of 60% sulfuric acid, and 120 g of benzene was mixed together for an hour and a half over a water bath at 65°. The product was removed, neutralized with a soda solution, desiccated with sodium sulfate, and distilled in vacuum. This yielded 70 g of the dienyne (V) as a mobile, transparent liquid with a b.p. of 70-72° at 4 mm.

n_D^{20} 1.5300; d_4^{20} 0.9563; MR_D 47.81; computed 44.89.

3.055 mg substance; 9.110 mg CO_2; 2.235 mg H_2O. 3.601 mg substance: 10.730 mg CO_2; 2.605 mg H_2O. Found %: C 81.38, 81.38; H 8.18, 8.10. $C_{10}H_{12}O$. Computed %: C 81.08; H 8.1.

Hydrogenation of the dienyne (V). 3 g of the freshly distilled dienyne (V) was dissolved in 25 ml of ethyl alcohol and then hydrogenated with platinum oxide. 1.90 liters of hydrogen were absorbed, 1.92 liters of hydrogen being required theoretically, to hydrogenate two double bonds and one triple bond. Fractional distillation yielded 2 g of 2-methyl-4-butyltetrahydropyrone (VI) as a mobile, transparent liquid with a b.p. of 79-80° and the characteristic, unpleasant odor of bedbugs.

n_D^{20} 1.4380; d_4^{20} 0.8522; MR_D 48.06; computed 47.82.

4.214 mg substance: 11.858 mg CO_2; 4.770 mg H_2O. Found %: C 77.04; H 12.66. $C_{10}H_{20}O$. Computed %: C 76.90; H 12.81.

Hydration of the dienyne (V). 500 g of 90% aqueous methanol was mixed together with 0.2 g of pyrogallol, 3 g of mercuric sulfate, one drop of concentrated sulfuric acid, and 80 g of the dienyne (V), and the mixture was vigorously stirred at 62-65° for 4 hours. Then another 5 g of mercuric sulfate was added in two portions (an hour apart), the total thus being 8 g. Most of the methanol was driven off in a 75-mm vacuum at a bath temperature of 45°. The product was carefully

neutralized with soda, extracted with ether, desiccated with sodium sulfate, and fractionated in vacuum. This yielded 81 g of the dienone (VII), with a b.p. of 98-101° at 4 mm; n_D^{20} 1.5050, containing a trace of the corresponding methoxy ketone. Further fractionation yielded 60 g of the pure dienone (VII) as a mobile, light-yellow liquid, with a b.p. of 94-95° at 3 mm, which polymerized upon standing.

n_D^{20} 1.5050; d_4^{20} 1.0080; MR_D 48.96; computed 46.99.

11.40 mg substance; 30.53 mg CO_2; 8.76 mg H_2O. 12.59 mg substance: 33.54 mg CO_2; 9.67 mg H_2O. Found %: C 72.56, 72.74; H 8.60, 8.59. $C_{10}H_{14}O_2$. Computed %: C 72.29; H 8.43.

The dienone does not yield crystalline derivatives with semicarbazide or 2,4-dinitrophenylhydrazine.

Hydrogenation of the dienone (VII). 4 g of the freshly distilled dienone (VII) was hydrogenated over a Pt catalyst in 20 ml of alcohol. 1.21 liters of hydrogen were absorbed. The hydrogenation of two double bonds theoretically requires 1.26 liters of hydrogen. This yielded 3.7 g of the ketone (VIII) as a mobile liquid with a peculiar odor, b.p. 94-95° at 8 mm.

n_D^{20} 1.4510; d_4^{20} 0.9541; MR_D 48.0; computed 47.83.

4.314 mg substance: 10.095 mg CO_2; 4.042 mg H_2O; 4.145 mg substance: 10.655 mg CO_2; 3.855 mg H_2O. Found %; C 70.06, 70.35; H 10.68, 10.51. $C_{10}H_{18}O_2$. Computed %: C 70.59; H 10.58.

The 2,4-dinitrophenylhydrazone of ketone (VIII) fused at 121-122° (from alcohol).

Ozonation of the dienone (VII). Ozonated oxygen was passed through a solution of 10 g of the dienone (VII) in 40 g of anhydrous chloroform for 18 hours at the rate of 4 liters per hour (ozone concentration = 6%). The ozonide was vigorously mixed for one hour at room temperature and for 6 hours at 55-60° with 40 ml of 3% hydrogen peroxide. The solution was neutralized with 13 g of soda and repeatedly extracted with ether, but almost no neutral products were found. The salt solution was evaporated to dryness, acidulated with 15 ml of concentrated sulfuric acid, and carefully extracted with ether. After the ether extract had been desiccated and the ether driven off, the residue of organic acids was distilled in vacuum (100 mm); this yielded 2.1 g of formic acid, which boiled at 100-105° at atmospheric pressure and exhibited the characteristic reaction with corrosive sublimate. The thick yellow residue left after the formic acid had been driven off in vacuum did not crystallize in the vacuum exsiccator. A qualitative test for lactic acid was negative, while a test with ferric chloride exhibited the yellow color that is characteristic of hydroxy acids. The product was distilled in vacuum, yielding 1.9 g of β-hydroxybutyric acid as a viscous, slightly yellowish liquid with a b.p. of 80-83° at 9 mm. Analysis of the silver salt and titration gave the following constants for the β-hydroxybutyric acid:

Found %: Ag 50.90; M 100.17. Computed %: Ag 51.35; M 104.4.

To provide final proof that this was β-hydroxybutyric acid, it was converted into crystalline crotonic acid. 0.9 g of β-hydroxybutyric acid and 8 ml of 3% sulfuric acid were slowly distilled, at first at normal pressure, and then in vacuum. This yielded 0.15 g of colorless crystals, which fused at 70-71° and exhibited no depression when mixed with known crotonic acid.

Synthesis of the piperidone (XVI). A mixture of 11 g of the dienone (VII), 115 g of aqueous ammonia (sp. gr. 0.91), and 20 ml of alcohol was shaken up for 20 minutes until a completely homogeneous solution was produced. The solution was then heated to 80° in an autoclave for 4 hours. The ammonia was driven off in vacuum, first in the cold, and then over a water bath at 45°. The solution

was neutralized with hydrochloric acid until its reaction was slightly acid, and the neutral products were extracted with ether, but practically nothing was found. The organic base was salted out with caustic soda, extracted with ether, desiccated with sodium sulfate, and distilled in vacuum. This yielded 8 g of the piperidone (XVI) as a mobile liquid with a characteristic amine odor and a b.p. of 116-117° at 5 mm, which turned yellow upon standing.

n_D^{20} 1.4950; d_4^{20} 1.0590; MR_D 49.25; computed 49.24.

5.290 mg substance: 12.690 mg CO_2; 4.365 mg H_2O. 4.645 mg substance: 11.190 mg CO_2; 3.935 mg H_2O. Found %: C 65.46, 65.74; H 9.23, 9.48. $C_{10}H_{17}O_2N$. Computed %: C 65.57; H 9.29.

The 2,4-dinitrophenylhydrazone of the piperidone (XVI) fused at 247-249° (from alcohol).

Synthesis of the piperidone (IX). A mixture of 60 g of the dienone (VII), 100 g of a 35% aqueous solution of methylamine, and 0.3 g of pyrogallol was heated to 70° in an autoclave for 2 hours. Mixing the dienone (VII) with the methylamine results in the evolution of considerable heat, and this operation is therefore performed with the vessel chilled. The excess methylamine was driven off at 45° in a 75-mm vacuum over a water bath. The solution was neutralized with hydrochloric acid until it was slightly acid, and the neutral products were extracted with ether, though the quantity recovered was negligible. The organic base was salted out with cuastic soda, extracted with ether, desiccated with sodium sulfate, and distilled in vacuum. This yielded 59.2 g of the piperidone (IX) as a mobile liquid with a characteristic amine odor and a b.p. of 110-113° at 3 mm, which turned yellow upon standing.

n_D^{20} 1.4980; d_4^{20} 1.0580; MR_D 54.18; computed 54.17.

7.215 mg substance: 17.746 mg CO_2; 6.415 mg H_2O. 3.535 mg substance: 8.700 mg CO_2; 3.256 mg H_2O. Found %: C 67.28, 67.16; H 9.97, 9.83. $C_{11}H_{13}O_2N$. Computed %: C 67.0; H 9.64.

The picrate of the piperidone (IX) fused at 228-230° (from alcohol).

Synthesis of the acetylenic piperidol (X). 2 g of powdered caustic potash and 50 ml of anhydrous ether were placed in a three-necked flask, fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser. The mixture was saturated with acetylene for 30 minutes at -2°. Then, with constant stirring and with acetylene constantly passing through the mixture, 3.2 g of the piperidone (IX) dissolved in an equal volume of ether was added drop by drop during the course of 35 minutes. The acetylene was passed through the mixture for another 8 hours at -2° after all the piperidone had been added. The condensation reaction does not take place at a temperature below -2°. The product was hydrolyzed with 10 ml of water and extracted with ether; a current of carbon dioxide was passed through the ether solution for 2 hours in order to remove the alkali, after which the product was desiccated with sodium sulfate and distilled in vacuum. This yielded 2.9 g of the acetylenic alcohol (X) as a yellowish, extremely viscous liquid with a b.p. of 139-141° at 5 mm, which hardened into a hyaline mass and softened when heated.

5.905 mg substance: 14.881 mg CO_2; 15.021 mg H_2O. Found %: C 69.42; H 9.54. $C_{13}H_{21}O_2N$. Computed %: C 69.95; H 9.41.

The hydrochloride of the acetylenic alcohol (X) fused at 121-213° after having been desiccated in a vacuum exsiccator above phosphoric anhydride. It is a hygroscopic, amorphous, white powder that deliquesces when exposed to the air and settles out as a viscous noncrystalline mass when an effort is made to recrystallize it.

Hydrogenation of the acetylenic piperidol (X). 1.5 g of the freshly distilled acetylenic alcohol (X) was hydrogenated above a Pd catalyst in 10 ml of alcohol. 240 ml of hydrogen was absorbed. Hydrogenation was complete in 20 minutes. This yielded the ethylpiperidol (XI) as a viscous, transparent liquid with a peculiar odor and a b.p. of 140-142° at 8 mm.

11.43 mg substance: 11.33 mg CO_2; 28.60 mg H_2O. 13.45 mg substance: 13.47 mg CO_2; 33.66 mg H_2O. Found %: C 68.27, 68.29; H 11.09, 11.20. $C_{13}H_{25}O_2N$. Computed %: C 68.72; H 11.12.

The hydrochloride of the ethylpiperidol (XI) is a white, amorphous, hygroscopic powder with a m.p. of 97-167°, which behaves like the preceding hydrochloride.

Synthesis of the vinylacetylenic piperidol (XII). 7.8 g of the piperidone (IX), dissolved in an equal volume of ether, was added drop by drop, with ice-water chilling, to vinylacetylenemagnesium bromide, prepared (as specified above) from 3 g of magnesium, 12 g of ethyl bromide, and 20 ml of vinylacetylene dissolved in 50 ml of absolute ether. Stirring was continued for 5 hours at room temperature and for one hour at the ether's boiling point. The product was hydrolyzed with concentrated hydrochloric acid (30 ml), and the ether solution was separated, but no neutral products were found. The aqueous solution of the salt of the organic base was saturated with caustic soda, and the product was extracted with ether and desiccated with sodium sulfate. Vacuum fractionation yielded 6.1 g of the vinylacetylenic piperidol (XII) with a b.p. of 150-155° at 3 mm.

3.550 mg substance: 9.370 mg CO_2; 2.910 mg H_2O. 3.760 mg substance: 9.915 mg CO_2; 3.055 mg H_2O. Found %: C 71.96, 71.94; H 9.17, 9.21. $C_{15}H_{23}O_2N$. Computed %: C 72.28; H 9.23.

This alcohol is a yellowish hyaline product that softens when heated (50-60°). Its hydrochloride is a hygroscopic white powder with a m.p. of 110-210°, titration of which yielded the following data:

0.0381 g substance: 2.3 ml 0.1 N KOH. 0.0692 g substance: 2.4 ml 0.1 N KOH. Found %: Cl 12.15, 12.09; $C_{15}H_{23}O_2N \cdot HCl$. Computed %: Cl 12.45.

Hydrogenation of the vinylacetylenic piperidol (XII). 2 g of the freshly distilled vinylacetylenic alcohol (XII), dissolved in 15 ml of ethyl alcohol, was hydrogenated with a Pd catalyst. The hydrogen absorbed totaled 500 ml instead of the 570 ml called for theoretically. This yielded 1.5 g of the butylpiperidol (XIII) as a transparent, viscous liquid with a peculiar odor and a b.p. of 137-140° at 3 mm.

11.87 mg substance: 12.14 mg CO_2; 30.35 mg H_2O. 13.68 mg substance: 14.07 mg CO_2; 34.92 mg H_2O. Found %: C 69.80, 69.71; H 11.44, 11.51. $C_{15}H_{29}O_2N$. Computed %: C 70.58; H 11.37.

The hydrochloride of this alcohol fused at 91-158° after having been desiccated in a vacuum exsiccator. It is an amorphous white product that settled out as a viscous noncrystalline mass when an effort was made to recrystallize it.

11.864 mg substance: 0.200 ml 0.025 N $AgNO_3$. 12.415 mg substance: 0.169 ml 0.025 N $AgNO_3$. Found %: Cl 11.89, 12.06. $C_{15}H_{29}O_2N \cdot HCl$. Computed %: Cl 12.21.

Synthesis of the phenylpiperidol (XIV). Phenyllithium was prepared from 1 g of small bits of metallic lithium and 12 g of bromobenzene dissolved in 50 ml of absolute ether in an atmosphere of nitrogen within a round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser. Stirring was continued in the nitrogen atmosphere for 2 hours at room temperature and for 30 minutes at the ether's boiling point. 9 g of the piperidone (IX), dissolved in an equal volume of ether, was added drop by drop at a temperature of -12° to the

phenyllithium thus produced. Stirring was continued for another 2 hours at room temperature and for 2 more hours with the ether at a boil. The product was hydrolyzed with 18% hydrochloric acid (80 ml), and after careful shaking in a separating funnel, the aqueous layer was removed and saturated with caustic soda; the product was extracted with ether, desiccated with sodium sulfate, and fractionated in vacuum. This yielded 8.9 g of the phenylpiperidol (XIV), a very viscous, yellowish liquid with a b.p. of 166-168° at 3 mm.

3.800 mg substance: 10.310 mg CO_2; 3.115 mg H_2O. 3.530 mg substance: 9.590 mg CO_2; 2.850 mg H_2O. Found %: C 74.04, 74.14; H 9.17, 9.03. $C_{17}H_{25}O_2N$. Computed %: C 74.19; H 9.09.

When chilled, the product hardened into a hyaline mass, which was pulverized into an amorphous powder that softened at 52-58°. The hydrochloride of this piperidol is a white amorphous product with a m.p. of 105-167°. Its behavior resembles that of the hydrochlorides of the piperidols described above.

Preparation of the acetate (XV, R = CH_3). A mixture of the phenylpiperidol (XIV), 30 ml of acetic anhydride (m.p. 138-140°) and one drop of concentrated sulfuric acid was allowed to stand for 8 hours at room temperature and then was heated for 2 hours to 70° over a water bath. The acetic anhydride was driven off in a 15-mm vacuum, and the residue was diluted with 2 ml of water and neutralized with sodium bicarbonate. The product was extracted with ether, desiccated with sodium sulfate, and fractionated in vacuum. This yielded 2.3 g of the acetate (XV, R = CH_3) with a b.p. of 158-161° at 1 mm, which solidified into a hyaline mass that softens when heated.

3.690 mg substance: 9.705 mg CO_2; 2.905 mg H_2O; 5.140 mg substance: 13.520 mg CO_2; 3.982 mg H_2O. Found %: C 71.77, 71.83; H 8.81, 8.67. $C_{19}H_{27}O_3N$. Computed %: C 71.78; H 8.51.

The hydrochloride of this product was a white, amorphous, hygroscopic mass with a m.p. of 142-177°.

0.1020 g substance: 2.67 ml 0.1 N KOH. 0.0890 g substance: 2.55 ml 0.1 N KOH. Found %: Cl 9.7, 10.14. $C_{15}H_{27}O_3N \cdot HCl$. Computed %: Cl 10.03.

Preparation of the propionate (XV, R = C_2H_5). A mixture of 2.6 g of the phenylpiperidol (XIV), 30 ml of propionic anhydride, and one drop of concentrated sulfuric acid was heated for 3 hours over a boiling water bath. The propionic anhydride was driven off in a 24-mm vacuum, and the residue was diluted with water (2 ml) and neutralized with sodium bicarbonate; the product was extracted with ether, desiccated with sodium sulfate, and fractionated in vacuum. This yielded 2.1 g of the propionate (XV, R = C_2H_5) with a b.p. of 172-174° at 2.5 mm as a yellow, amorphous, hyaline mass, which softens when heated (52-55°).

10.00 mg substance: 7.70 mg CO_2; 26.63 mg H_2O. 10.33 mg substance: 8.00 mg CO_2; 27.50 mg H_2O. Found %: C 72.67, 72.65; H 8.65, 8.64. $C_{20}H_{29}O_3N$. Computed %: C 72.50; H 8.76.

The hydrochloride of this ester fuses at 150-175°. It is a white amorphous product, which settles out as an oil when recrystallized:

0.096 mg substance: 2.65 ml 0.1 N KOH. Found %: Cl 9.78. $C_{20}H_{29}O_3N \cdot HCl$. Computed %: Cl 9.65.

SUMMARY

An 80% yield of 2-methyl-4-vinylethynyl-4-pyranol (III) has been secured by reacting 2-methyltetrahydro-4-pyrone (II) with vinylacetylenemagnesium bromide; the product is smoothly dehydrated in benzene solution to the dienyne (V) by means

of 60% sulfuric acid. When the dienyne is heated in aqueous solutions of methanol with mercurous sulfate, it is hydrated to the dienone (VII), the yield being approximately 90%.

Reacting the dienone (VII) with methylamine and ammonia results in a high yield (as much as 95%) of bicyclic γ-piperidones (IX and XVI), which contain a condensed tetrahydropyran ring.

Condensation of the piperidone (IX) with acetylene and vinylacetylene results in high yields of the acetylenic and vinylacetylenic piperidols (X and XII), respectively.

Reacting the piperidone (IX) with phenyllithium results in a high yield of the phenylpiperidol (XIV), which is converted into the respective esters (XV) by the action of acetic and propionic anhydrides.

All the unsaturated compounds described above were hydrogenated to the respective saturated compounds with a Pd catalyst.

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THE ADDITION OF DIALKYL PHOSPHOROUS ACIDS TO UNSATURATED COMPOUNDS

I. THE ADDITION OF DIALKYL PHOSPHOROUS ACIDS TO β,β-DIMETHYL DIVINYL KETONE

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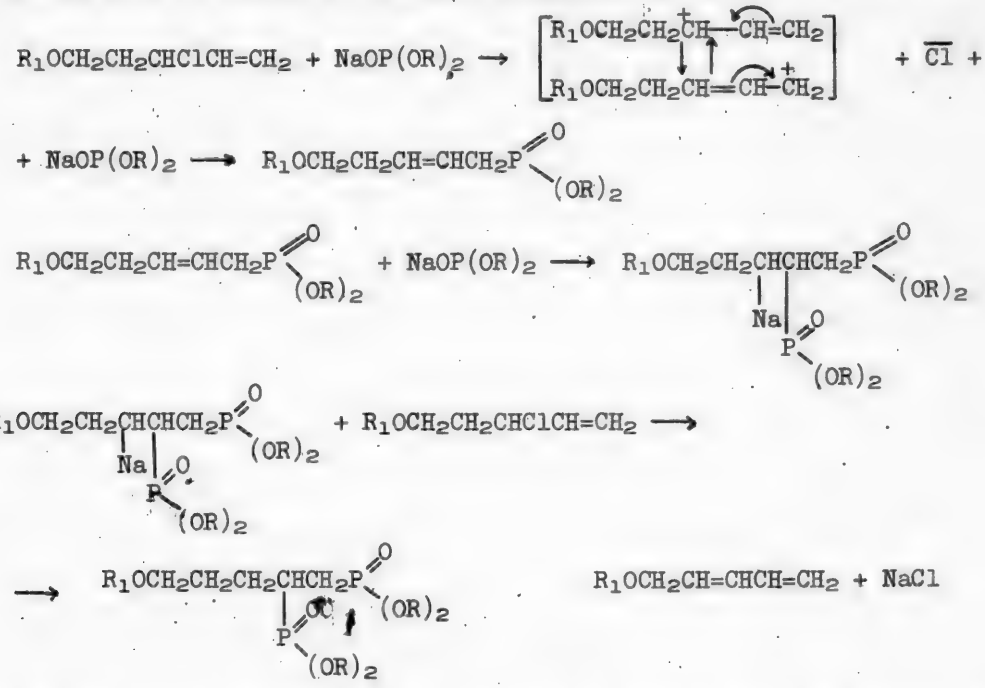
In one of our previous reports [1] we made a study of the action of salts of dialkyl phosphorous acids upon allyl halide isomers. We showed that this not only entails the formation of esters of alkoxy ethyl allyl phosphorous acids, normally for primary allyl halide compounds and with a complete allyl rearrangement for secondary allyl halides, but the further addition to them of a sodium dialkyl phosphite, giving rise to alkoxy di-(dialkyl phosphono)-pentanes.



Inasmuch as the cited instance of the addition of sodium salts of dialkyl phosphorous acids to unsaturated compounds is the only one known in the literature up to the present time and is of considerable theoretical interest, we resolved to make a study of this new type of reaction, as applied to unsaturated compounds belonging to various groups of organic compounds.

The present paper describes the results obtained in our study of the addition

of dialkyl phosphorous acids to β,β-dimethyl divinyl ketone, which is an unsaturated ketone. As the researches of I.N.Nazarov and his associates have shown, the divinyl ketones are extremely reactive compounds. They succeeded, for instance, in adding water, alcohols, amines, diene hydrocarbons, malonates and acetates, furan derivatives, hydrogen chloride, and hydrogen sulfide to β,β-dimethyl divinyl ketone [2]. The addition reaction is selective; most compounds are added at an unsubstituted vinyl group, while others, such as hydrogen chloride and hydrogen sulfide, on the contrary, are added principally at a substituted vinyl group.

We tested the addition of dialkyl phosphorous acids to β,β-dimethyl divinyl ketone under various conditions. In our first experiments we added a solution of a sodium dialkyl phosphite to the dialkyl phosphorous acid; the reaction was very violent, but the yield of addition products was insignificant and quite undependable. We later learned that the best results are obtained by adding a small quantity of an alcoholic solution of a sodium alcoholate to the mixture of the ketone and the dialkyl phosphorous acid, as was the case in several reactions investigated by I.N.Nazarov and his co-workers. When this procedure was used, the reproducibility of the results and the product yields were wholly satisfactory. We made a study of the addition of dimethylphosphorous, diethylphosphorous, diisobutylphosphorous, and dibutylphosphorous acids to β,β-dimethyl divinyl ketone. The addition of dimethyl- and diethylphosphorous acids is most vigorous, the temperature of the reaction mixture rising to 80-90° after a few drops of the alcoholic solution of the alcoholate had been added to it, and the reaction being practically complete in a few minutes. The addition of the higher dialkyl phosphorous acids is somewhat less lively and requires a much larger quantity of the sodium alcoholate.

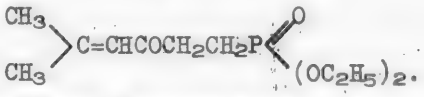
The constants and yields of the addition products are given in the table.

TABLE

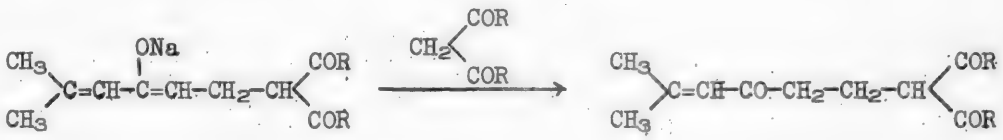
Serial No.	Formula	B.p.	n_D^{20}	d_4^{20}	Yield, %
1	$(CH_3)_2C=CHCOCH_2CH_2P(=O)(OCH_3)_2$	169-171° at 13 mm	1.4711	1.1130	59
2	$(CH_3)_2C=CHCOCH_2CH_2P(=O)(OC_2H_5)_2$	149° at 3 mm	1.4660	1.0658	52
3	$(CH_3)_2C=CHCOCH_2CH_2P(=O)(OC_4H_9iso)_2$	188-190° at 10 mm	1.4511	1.0013	48.5
4	$(CH_3)_2C=CHCOCH_2CH_2P(=O)(OC_4H_9\text{-}N)_2$	198-200°	1.4623	1.0111	57

A thorough study was made of the addition product of diethylphosphorous acid and β,β-dimethyl divinyl ketone in order to ascertain the structure of the resulting products. Titration of the product with a bromine solution indicated that it contained only one double bond. Saponification of the product with hydrochloric acid yielded ethyl chloride, the amount corresponding to that computed theoretically on the basis of the molecule having one diethylphosphono group. The presence of one diethylphosphono group in the molecule was also borne out by titrating the phosphinic acid produced by saponification with an alkali solution. No phosphoric

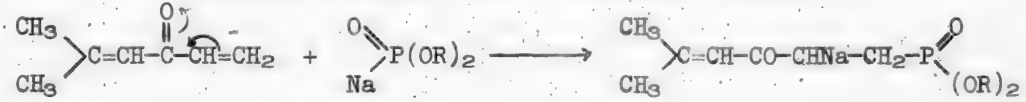
acid was found in the saponification products, though it should have been formed during saponification if the phosphorus of the phosphono group were connected directly to a carbon atom that was in an α-position to the ketone group [3]. (Reacting the acid with phenylhydrazine yielded a crystalline product with a m.p. of 143-144°; the addition product of phenylhydrazine and phosphoric acid has a m.p. of 155-156° with swelling; a mixed test sample of the two products fused at 130°.) Lastly, oxidizing the product with potassium permanganate yielded a large quantity of acetone, the semicarbozone of which fused at 176°. The fact that the product in question had a ketone group was proved by color reactions with sodium nitroprusside and by β-naphthol with sulfuric acid, as well as by the formation of a liquid phenylhydrazone, which distilled at 210° at 2 mm. These data indicate that the addition product of diethylphosphorous acid and β,β-dimethyl divinyl ketone has the following formula:

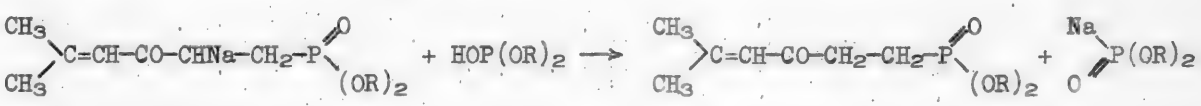


As for the mechanism of the reaction we have studied, we believe the following is true. I.N.Nazarov and L.Terekhova think that the addition of malonates, acetates and acetylacetone to β,β-dimethyl divinyl ketone involves the formation of the corresponding sodium derivatives, followed by their addition to the unsaturated ketone at the 1,4-position as follows:



But since our experiments have shown that dialkyl phosphorus acids are added not only to unsaturated ketones, but to unsaturated phosphinic esters as well, to which the foregoing scheme (1,4 addition) does not apply at all, it is probable that the addition takes place directly, at the 1,2 position, as follows.





EXPERIMENTAL

Addition of diethylphosphorous acid to β,β-dimethyl divinyl ketone. Experiment 1. A small bit of metallic sodium (the size of a pinhead) was dissolved in 14 g of diethylphosphorous acid. Then the solution was gradually added to 11 g of β,β-dimethyl divinyl ketone. The reaction involves the evolution of a large amount of heat, the mixture growing very hot. To keep the temperature of the reaction

mixture down, it was cooled with cold water throughout the addition of the diethylphosphorous acid. After all the diethylphosphorous acid had been added, the reaction mixture was heated over a water bath for 3 hours, and then it was distilled in vacuum from an Arbuzov flask. The first fractionation yielded 13 g of a fraction that boiled at 159-165° at 5 mm. Some 10 g of an extremely viscous transparent yellow liquid. Efforts to distil it at 2 mm failed; intense heat caused it to decompose, giving off a large quantity of white vapor. Analysis of this residue indicated it contained 13% of phosphorus, whereas the product of the addition of two molecules of diethylphosphorous acid to β,β-dimethyl divinyl ketone ought to contain 16.1%. Most of the 159-165° (5 mm) fraction boiled at 149° at 2 mm when refractionated.

d_4^{20} 1.0658; n_D^{20} 1.4660. 0.1704 g substance: 38.7 ml NaOH (T = 0.0200). P 12.2%. $C_{12}H_{21}O_4P$. Computed %: P 12.5.

In a second experiment, the reaction was carried out in an ether solution; the results were the same as before. In a series of similar experiments we secured a much smaller amount of the addition product; chiefly the undistillable product referred to above was secured.

Experiment 2. A few drops (about 10) of a saturated alcoholic solution of sodium ethoxide were added gradually, from a dropping funnel, to a reaction mixture consisting of 14 g of diethylphosphorous acid and 11 g of β,β-dimethyl divinyl ketone, chilled with cold water. The reaction was very violent, the reaction mixture being heated considerably. Further addition of sodium ethoxide causes no heating up of the reaction mixture, however. After the reaction mixture had been heated over a water bath for two hours, it was transferred to an Arbuzov flask and distilled in vacuum. This yielded 14 g of a product with a b.p. of 176-180° at 11 mm; n_D^{20} 1.4668: Residue - 8.7 g.

Investigation of the product with a b.p. of 149° at 2 mm. The product is a rather viscous liquid, slightly yellowish, soluble in water and various organic solvents.

Titration with bromine. The number of double bonds in the product was determined quantitatively by the MacIlinney method. 0.4050 g substance: hyposulfite used (for addition) 36.3 ml (T = 0.017008). 0.30 g of bromine was added. Computed for F_1 0.27 g.

Saponification. 6 g of the product was heated with 30 ml of dilute (1:1) hydrochloric acid to 170-180° for 10 hours in a sealed tube. After the tube was opened, the ethyl chloride was evaporated. Its residual traces in the reaction mixture were removed by warming the tube in warm water. The difference in the tube's weight before and after the ethyl chloride had been removed totaled 3.3 g. On the assumption of one phosphono group, 3.1 g of ethyl chloride should have been evolved theoretically. The aqueous solution was repeatedly evaporated in a porcelain dish with distilled water after the ethyl chloride had been driven off. After all the hydrogen chloride had been driven off, the water was driven off in vacuum. The residue consisted of phosphinic acid as a thick liquid. It was allowed to stand for a month in an exsiccator above sulfuric acid. No crystallization occurred. A total of 4.8 g of the acid was recovered. 6 g of the phosphinic ester should have yielded 4.7 g. 4.2 g of the acid was dissolved in water and titrated with an alkali solution. All the acid (4.7 g) should have required 1.98 g of NaOH, whereas the recomputed actual quantity consumed was 2.15 g. 0.6 g of phenylhydrazine was added to 0.6 g of the acid, weighed in a tiny porcelain dish and diluted with 5 ml of ethyl alcohol. A copious precipitate settled out within a few minutes. It was filtered out and desiccated. A crystalline mass totalling 0.75 g was recovered. The substance fused at 143-144° without

swelling after having been twice recrystallized from alcohol. The addition product of phenylhydrazine and phosphoric acid fuses at 155-156° with much swelling. A mixed test sample of the two substances fused at 130°.

Oxidation. 2.8 g of the product was dissolved in 200 ml of water, and 3.8 g of powdered potassium permanganate was gradually added with constant stirring and cooling with running water. The solution was decolorized after standing for a day above manganese dioxide; the whole mass was transferred to a flask and 15 ml of the total was driven off. The distillate had the characteristic odor of acetone. Semicarbazide was added to it, after which the mixture was allowed to stand for a day. The semicarbazone began to settle out within 10 minutes after the semicarbazide had been added. A total of 0.3 g of acetone semicarbazone, with a m.p. of 176°, was secured. After the manganese dioxide had been filtered out, the aqueous solution of the salt was evaporated nearly to dryness, the salt was decomposed by adding sulfuric acid, and the free acids were extracted with ether. The ether was driven off, and the residue was distilled in vacuum from a small flask; we were unable to collect a fraction with a definite boiling point.

Action of phenylhydrazine. 5 ml of absolute ethyl alcohol and 1.5 g of free phenylhydrazine were added to 3 g of the addition product. The reaction mixture was set aside to stand at room temperature, and then in the cold for 15 days. No crystallization was observed. Vacuum fractionation of the mixture yielded some 2 g of the phenylhydrazone with a b.p. of 210° at 2 mm, as an extremely viscous oil.

0.2858 g substance: consumed 47.25 ml NaOH (T = 0.02000).
0.3390 g substance: consumed 54.5 ml NaOH. Found %: P 9.15, 8.9.
$C_{17}H_{27}O_3N_2P$. Computed %: P 9.20.

Addition of dimethylphosphorous acid to β,β-dimethyl divinyl ketone. A few drops of a saturated alcoholic solution of sodium ethoxide were gradually added from a dropping funnel, with constant chilling, to a mixture consisting of 11 g of β,β-dimethyl divinyl ketone and 11 g of dimethylphosphorous acid. The addition of each drop caused the evolution of considerable heat in the reaction mixture. A total of 10 drops had to be added for the reaction to be practically complete. Then the reaction mass was heated for 3 hours and fractionated in vacuum. Two fractionations resulted in the recovery of 13 g of a product with a b.p. of 169-171° at 3 mm.

d_4^{20} 1.1130; n_D^{20} 1.4711. 0.1204 g substance: consumed 31.2 ml NaOH (T = 0.02000). 0.2026 g substance: consumed 50.6 ml NaOH. Found % P 14.3, 13.8. $C_9H_{17}O_4P$. Computed %: P 14.1.

Addition of diisobutylphosphorous acid to β,β-dimethyl divinyl ketone. A solution of sodium ethoxide was added drop by drop to a reaction mixture consisting of 8 g of β,β-dimethyl divinyl ketone and 14 g of diisobutylphosphorous acid, chilled with water. Completion of the reaction required much more sodium ethoxide than in the addition of the dimethyl- and diethylphosphorous acids. Fractionation of the reaction mixture yielded 10.7 g of product.

B.p. 188-190° at 10 mm; d_4^{20} 1.0013; n_D^{20} 1.4511.

0.1629 g substance: consumed 30.2 ml NaOH (T = 0.0200). 0.1589 g substance: consumed 29.7 ml NaOH. Found %: P 10.2, 10.3.
$C_{15}H_{29}O_4P$. Computed %: P 10.2.

Addition of dibutylphosphorous acid to β,β-dimethyl divinyl ketone. The reaction was carried out according to the procedure specified for the preceding experiments, using 10 g of the ketone and 18 g of the dibutylphosphorous acid. Fractionation of the reaction mixture yielded 16 g of the product.

B.p. 198-200° at 12 mm; d_4^{20} 1.0111; n_D^{20} 1.4623.

0.1536 g substance: consumed 27 ml NaOH (T = 0.02034).
Found %: P 9.96. $C_{15}H_{29}O_4P$. Computed %: P 10.20.

SUMMARY

It has been shown that in the presence of small quantities of alcoholates of the alkali metals dialkyl phosphorous acids are readily added to β,β-dimethyl divinyl ketone, producing the respective esters of phosphinic acid. The structure of the resulting products has been demonstrated, and the mechanism of thier formation is suggested.

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DECOMPOSITION OF α-HALOGEN ETHERS

I. α-HALOGEN ETHYL ALKYL ETHERS

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The results of an investigation of the properties and transformations of α-halogen ethers, set forth in our previous reports [1,2], have shown that these compounds are extremely unstable substances that are readily decomposed, as had been noted in the earlier researches by Farren and Cocker [3,4].

The unusual tendency of alpha halogen ethers to break down spontaneously has made the investigation of these compounds extremely difficult, so that we had to solve the problem of stabilizing them. We found, after a series of experiments, that adding 15% of benzene, dioxane, or sulfuric ether to the α-halogen ethers makes it possible to keep them for more than 2 months instead of the few hours when they are stored in the pure state.

The authors mentioned above [3,4] point out that the decomposition of α-halogen ethyl alkyl ethers is accompanied by the evolution of a hydrohalide and the formation of tarry products.

The study we undertook of the decomposition of α-halogen ethyl alkyl ethers has established that there are several types of decomposition of these compounds, depending upon the reaction conditions. We also found that a decomposition involving the evolution of a free hydrohalide occurs only in the hydrolytic decomposition of α-halogen ethyl alkyl ethers and, hence, is not a spontaneous decomposition of these substances. α-Halogen ethyl alkyl ethers fume as soon as atmospheric moisture reaches them, undergoing hydrolytic cleavage, forming a hemiacetal, which breaks down spontaneously into acetaldehyde and an alcohol.

Exposure to atmospheric moisture causes a number of side reactions to take place (owing to the fact that not enough water is present), particularly, the reaction of the α-halogen ethyl alkyl ethers with the evolved alcohol, resulting in the formation of acetals, as has been shown by Shostakovsky and Tupaev. Considerable tarring also occurs, apparently at the expense of the acetaldehyde that is formed. The hydrolytic decomposition of α-halogen ethers takes place instantaneously when water is present in excess [1,2,5], a hydrohalide, acetaldehyde, and an alcohol being formed quantitatively; this may serve as a model of an ionic reaction. We have used the hydrolytic decomposition of α-halogen ethers with an excess of water as a basis for the elaboration of methods for quantitatively determining these compounds by titrating them with: a) a standard alkali solution; b) a solution of silver nitrate; and c) by the bisulfite method. The methods we propose all yield comparable results that agree with the quantitative determinations of the α-halogen ethers based upon the results of elementary analysis (Table 1 and 2).

TABLE 1

Quantitiative Determination of the α-Halogen Ethers

No.	Formula	Titration by the bisulfite method		Titration with 0.1 N NaOH		Volhard titration	
		g CH_3CHO		Acid equivalent		Per cent halogen	
		Found	Computed	Found	Computed	Found	Computed
1	$CH_3-CHCl-OC_2H_5$	43.61	44.0	111.2	108.5	32.12	32.70
2	$CH_3-CHCl-OC_4H_9$	43.94	44.0	136.5	136.5	25.40	25.96
3	$CH_3-CHCl-OC_6H_5$	43.86	44.0	157.3	156.5	22.55	22.68
4	$CH_2Cl-OC_4H_9$	29.58	30.0	123.0	122.5	27.92	28.98
5	$CH_3-CHBr-OC_4H_9$	43.12	44.0	183.1	180.9	43.50	44.17

TABLE 2

Quantitative Determination of α-Halogen Ethers by Various Methods

No.	Formula	Titration with 0.1N NaOH	Volhard titration	Carius combustion of the halogen	Bisulfite method
1	$CH_3-CHCl-OC_4H_9$	99.15	99.08	–	99.80
2	$CH_3-CHCl-OC_6H_5$	99.58	99.03	99.40	99.50
3	$CH_3-CHBr-OC_4H_9$	98.45	99.30	98.01	98.60

We likewise investigated the decomposition of α-halogen ethers occurring: 1) when the temperature is raised (thermal decomposition); and 2) as the result of the action of light, in sealed ampoules: a) in the pure state; b) in a solvent medium; and c) in reagents that combine with the hydrohalide.

We found that α-halogen ethyl alkyl ethers always decompose by giving rise to an alkyl halide, water, and a tarry product. The alkyl halide and water are evolved quantitatively; the tarry product contains considerable oxygen, which may be due to the oxidation of the resulting acetylene residue during polymerization. This decomposition of the α-halogen ethyl alkyl halides is observed when they are distilled at atmospheric pressure and when they are kept in sealed ampoules in diffuse light at room temperature. We did not notice any evolution of acetaldehyde, except for a single instance, where we detected traces of acetaldehyde in the initial fraction. This contradicts the researches of Farren, Cocker, and Straus [3,4,6], who describe the evolution of nothing but acetaldehyde and an alkyl halide under similar conditions.

The production of an alkyl halide and water when α-halogen ethers are decomposed may be regarded as the result of a secondary reaction between the resultant hydrohalide and alcohol, as follows:

$$CH_3-CHHal-OR \longrightarrow HHal + ROH + (CH=CH) \downarrow \text{tar}$$

$$HHal + ROH \rightarrow RHal + H_2O.$$

To test the possibility of such a reaction, we decomposed α-bromoethyl butyl ether in allyl bromide, which we know can combine with free hydrogen bromide. The mixture of the α-halogen ether and the allyl bromide was kept exposed to light for 3 weeks in a sealed ampoule; the reaction mixture turned dark, which was an external sign that decomposition had occurred. And, indeed, vacuum fractionation quantitatively yielded an alkyl halide, water, and a tarry residue, all the allyl bromide being recovered. Thus, the supposition that a free hydrohalide is evolved

was not borne out, and the resulting products must be regarded as the primary products of the decomposition reaction.

The instability of α-halogen ethyl alkyl ethers when exposed to sunlight supports the notions concerning the oxonium nature of these compounds [7]. We know, for instance, of the decomposition of unsaturated ethers under similar conditions when reacted with hydrohalic acids [8].

EXPERIMENTAL

I. Investigation of the conditions and nature of the decomposition of α-bromoethyl butyl ether – CH_3–CHBr–OC_4H_9. α-Bromoethyl butyl ether, synthesized by hydrobrominating vinyl butyl ether [2] and possessing the following constants:

B.p. 63.0-63.8° (21 mm); n_D^{20} 1.4483; d_4^{20} 1.2081; MR_D 39.60; computed 39.31.

was used in all the experiments of the present investigation.

0.1664 g substance: 20.0 ml 0.1 N $AgNO_3$; 10.96 ml 0.1 N NH_4CNS.
0.1853 g substance: 20.0 ml 0.1 N $AgNO_3$; 10.88 ml 0.1 N NH_4CNS.
0.1467 g substance: 8.02 ml 0.1 N NaOH. 0.1464 g substance: 7.97 ml 0.1 N NaOH. Found %: Br 43.42, 43.65; equiv. 182.9, 183.3. $C_8H_{13}OBr$. Computed %: Br 44.17; equiv. 180.9.

1) Thermal decomposition of α-bromoethyl butyl ether. 180 g of the ether was placed in a Favorsky flask connected to a 25-cm herringbone dephlegmator. The flask was attached to the condenser, the latter being connected to a system of receivers for tapping off the liquid and gaseous products. The contents of the flask were heated over Wood's alloy. Distillation began at 82° and ended at 120°. Slow distillation yielded the following fractions: I – b.p. 82-96°, 0.5 g; II – 96-118°, 147 g; III – 118-120°, 2.0 g; 28 g of a dark residue. Traces of acetaldehyde were found in Fraction I (reaction with fuchsin sulfurous acid). Fraction II consisted of two layers; the separation and fractionation of which yielded 132 g of a product having the following constants:

B.p. 100-105°; n_D^{20} 1.4390; d_4^{20} 1.2786; MR_D 28.30; computed 28.37.

This product was butyl bromide; its constants agreed with those given in the handbooks. Its yield in this experiment was 97.1% of the theoretical. The top layer of Fraction II, which totaled 15 g, consisted of water: b.p. 100°; d_4^{20} 0.9981. (It was colored blue by $CuSO_4$, it mixed with alcohol, and it reacted with metallic sodium). No traces of acetaldehyde were found in the receiver designed for gaseous products.

2) Decomposition of the α-bromoethyl butyl ether by diffuse light. 20 g of the ether was sealed in a 50-ml ampoule and exposed to diffuse light at room temperature. The product turned dark after three days of exposure. The ampoule was chilled and then opened, its contents being transferred to a Favorsky distillation flask attached to a 6-cm herringbone dephlegmator. Distillation was effected over Wood's alloy, using a low vacuum to prevent thermal decomposition. This yielded a fraction with a b.p. of 68-71° (150 mm), consisting of two layers: a lower layer totaling 12.1 g, and an upper layer of 2.0 g. A dark tarry residue totaling 4.6 g was left in the flask. The bottom layer of the distillate was washed twice with water, desiccated above calcined Na_2SO_4, and distilled at normal pressure. The constants of the resulting product were:

B.p. 100.5-101°; n_D^{20} 1.4380; d_4^{20} 1.2983; MR_D 27.60; computed 28.37.

This product is butyl bromide; its yield totaled 80.1% of the theoretical. The upper layer of the distillate consisted of water, it presence being proved as

in the preceding experiment.

3) Decomposition of α-bromoethyl butyl ether in allyl bromide. 39.6 g of the ether and 13 g of allyl bromide (b.p. 70-71°) were sealed into a 100 ml ampoule and exposed to the light at room temperature for 3 weeks. The mixture darkened; fractionation of the mixture yielded the following fractions: I – b.p. 61-84°, 12.5 g; II – b.p. 84-95°, 32.3 g; and a residue of 6.7 g. Fraction I was desiccated above calcium chloride and then redistilled, after which its constants were as follows: b.p. 69.5-70°; n_D^{20} 1.4650; d_4^{20} 1.3972. This product was allyl bromide, 96% of the quantity used for the reaction being recovered.

Fraction II consisted of two layers: the lower layer, totaling 29.5 g, had the following constants after desiccation above calcium chloride and redistillation: b.p. 100.5-101° (normal pressure); n_D^{20} 1.4385; d_4^{20} 1.2987. This product was butyl bromide; its yield was 98.7% of the theoretical. The upper layer of Fraction II consisted of water (2.8 g). The residue was a dark, solid tar. Traces of acetaldehyde were found in the traps set up for gaseous products. The total acetaldehyde was determined by the bisulfite method [1]; it was 0.146 g. The other fractions gave a negative reaction for aldehydes with fuchsin sulfurous acid.

II. Investigation of the conditions and nature of the decomposition of α-bromodiethyl ether, $CH_3-CHBr-OC_2H_5$. In the experiments described below we used an α-bromodiethyl ether synthesized by hydrobrominating vinyl ethyl ether [2], its constants being:

B.p. 45-45.5° (55 mm); n_D^{20} 1.4462; d_4^{20} 1.2766; MR_D 31.93; computed 30.08. 0.3200 g substance: 25.0 ml 0.1 N $AgNO_3$; 4.42 ml 0.1 N NH_4CNS. 0.3108 g substance: 25.0 ml 0.1 N $AgNO_3$; 4.65 ml 0.1 N NH_4CNS. 0.3311 g substance: 20.99 ml 0.1 N NaOH. 0.3208 g substance: 20.57 ml 0.1N NaOH. Found %: Br 52.40, 52.33; equiv. 152.9, 155.6. C_4H_9OBr. Computed %: Br 52.26; equiv. 152.9.

1) Thermal decomposition of α-bromodiethyl ether. 25 g of the ether was placed in the apparatus used for the thermal decomposition of α-halogen ethers. Slow distillation yielded the following fractions: I – b.p. 50-62°, 16 g; II – b.p. 62-80°, 1.5 g; and a residue of 7.0 g. Fraction I exhibited a faint aldehyde reaction with fuchsin sulfurous acid. This fraction was redistilled after having been washed three times with distilled water and desiccated above calcined sodium sulfate, its constants then being:

B.p. 38.0-38.5°; n_D^{20} 1.4200; d_4^{20} 1.4310; MR_D 19.26; computed 19.20.

This product is ethyl bromide; its yield was 89% of the theoretical in this test.

Fraction II gave a negative aldehyde reaction with fuchsin sulfurous acid; it consisted of water that had a faint acetal odor. Acetaldehyde was detected by means of fuchsin sulfurous acid in the first of the two traps set up for the gaseous fractions. The tarry residue was dark and dissolved partially in ether and acetone.

III. Investigation of the decomposition of α-bromoethyl methyl ester, $CH_3-CHBr-OCH_3$. In this investigation we used an α-bromoethyl methyl ether synthesized by hydrobrominating vinyl methyl ether [2] and possessing the following constants.

B.p. 56.5-57° (185 mm); n_D^{20} 1.4486; d_4^{20} 1.4253; MR_D 26.11; computed 25.46. 0.1360 g substance: 24.51 ml 0.1 N $AgNO_3$; 14.74 ml 0.1 N NH_4CNS. 0.1566 g substance: 24.51 ml 0.1 N $AgNO_3$; 13.26 ml 0.1 N NH_4CNS. 0.1261 g substance: consumed 8.909 ml 0.1 N NaOH. 0.1379 g substance: consumed 9.779 ml 0.1 N NaOH. Found %: Br 57.06, 57.16; equiv. 141.54, 141.01. C_3H_7OBr. Computed %: Br 57.54. equiv. 138.9.

1) Decomposition of α-bromoethyl methyl ether by diffuse light. 25 g of the ether was sealed into a 50-ml ampoule and exposed to diffuse light for 3 weeks at room temperature. The contents of the ampoule turned dark and divided into layers. The ampoule was chilled and opened, the product being transferred to a Wurtz distilling flask. The product was distilled over a water bath at normal pressure, gaseous fractions also being collected. The following fractions were recovered: I – up to 34°, 3.8 g; II – 34-62°, 8.9 g; and a residue of 10.4 g. Water condensed on the walls of the receivers and the adapter. Fraction I consisted of a heavy oily liquid, which threw down a white jellylike precipitate with water. When sealed into an ampoule this liquid vaporized completely at +5°, recondensing to a liquid at +4°. This property of the product enables us to identify it as methyl bromide [2], which forms a hydrate with water that looks like a white jellylike precipitate. Fraction I exhibited a positive Beilstein test for halogens; the fuchsin sulfurous acid test for aldehydes was negative. Fraction II yielded methyl bromide as its hydrate, together with water and 0.3 g of a product with the following constants: b.p. 62-64°; n_D^{20} 1.3770. This product was dimethyl acetal [3]. The residue consisted of a dark tar, part of which dissolved in hot water. The portion that did not dissolve was pulverized in a mortar and washed with warm water until the wash waters gave a negative reaction for halogens. Then the tar was desiccated in a vacuum exsiccator and analyzed. The Beilstein test for halogens was positive.

5.250 mg substance: 12.637 mg CO_2; 3.215 mg H_2O. 4.515 mg substance: 11.058 mg CO_2; 2.705 mg H_2O. 0.1945 g substance: 18.7 g dioxane: Δt 0.08°. 0.3480 g substance; 18.7 g dioxane: Δt 0.145°. Found %: C 65.72; 65.48; H 6.85, 6.58; M 650.1, 641.7.

This product may be regarded as an aldehydic resin containing bromine. Our research is being continued.

SUMMARY

1. A study has been made of the conditions governing the decomposition of α-halogen ethyl alkyl ethers by increased temperature, by light, and by moisture.

2. Contrary to the existing assertions in the literature, α-halogen ethyl alkyl ethers evolve hydrohalides only when they react with moisture and with an excess of water.

3. The method of decomposing the α-halogen ethers by increasing the temperature or by exposure to light may be recommended as a simple way of preparing individual alkyl halides.

4. The behavior of α-halogen ethyl alkyl ethers when exposed to heat, light, and water conforms with the classical assertions of the oxonium theory concerning the properties of these compounds.

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DECOMPOSITION OF α-HALOGEN ETHERS

II. α-HALOGEN ETHYL PHENYL ETHERS

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In our last report [1] we set forth the results of an investigation of the decomposition of α-halogen ethyl alkyl ethers under various conditions. This investigation was extended to the α-halogen ethyl phenyl ethers, which were likewise prepared by the hydrobromination of vinyl phenyl ether [2]. Whereas α-halogen ethyl alkyl ethers are decomposed into an alkyl halide, water, and a tarry residue by the action of heat or light, the α-halogen ethyl phenyl ethers decompose under these conditions to yield a hydrohalide and a solid, brittle substance, from which we recovered a product that is quite similar to the products of a phenol-acetaldehyde condensation polymerization:

$$\underline{n}CH_3-CHHal-OC_6H_5 \longrightarrow \underline{n}HHal + (CH_2=CH-OC_6H_5)_{\underline{n}} \downarrow \text{resin}$$

α-Halogen ethyl phenyl ethers were observed to decompose thermally, by exposure to diffuse light at ordinary temperature in sealed ampoules, and by keeping them in an atmosphere of dry air. No acetaldehyde was found to have been evolved in any of the experiments. The circumstance that in a vinyl butyl ether medium α-halogen ethyl phenyl ethers decompose into products from which butyl bromide and a resin have been isolated is of interest. The formation of butyl bromide gives an idea of the mechanism involved in the decomposition of an α-halogen ethyl phenyl ether, which takes place via a stage in which the vinyl butyl ether is activated by the liberated hydrohalide [3].

a) $CH_3-CHHal-OC_6H_5 \longrightarrow HHal + (CH_2=CH-OC_6H_5)$;

b) $CH_2+CH-OC_4H_9 + HHal \longrightarrow (CH_2=CH-\underset{\displaystyle H}{O}-C_4H_9)^+Hal^-$;

c) $(CH_2=CH-\underset{\displaystyle H}{O}-C_4H_9)^+Hal^- \longrightarrow C_4H_9Hal + H_2O + (\underset{|}{\overset{|}{CH}}-\underset{|}{\overset{|}{CH}}) \downarrow \text{resin}$;

d) $CH_2=CH-OC_4H_9 + H_2O \longrightarrow CH_3CHO + C_4H_9OH$;

e) $CH_2=CH-OC_6H_5 + CH_3CHO \longrightarrow$ resin.

These transformations resemble the double decompositions of oxonium coordination compound [4]. The difference between our observation and the one that is generally known is that the hydrohalogenation of vinyl ethers is irreversible, the vinyl phenyl ether resulting after the hydrohalide has been removed undergoing polymerization under these conditions.

α-Halogen ethyl phenyl ethers are readily decomposed hydrolytically like the

α-halogen ethyl alkyl ethers. When water is present in excess, the hydrolytic decomposition is instantaneous, which makes it possible to titrate the decomposition products with a standard alkali solution or silver nitrate, and to use the bisulfite method for their quantitative determination.

EXPERIMENTAL

I. Investigation of the decomposition of α-bromoethyl phenyl ether (CH_3-$CHBr$-OC_6H_5). In these experiments we used an α-bromoethyl phenyl ether prepared by hydrobrominating vinyl phenyl ether [2] and possessing the following constants:

b.p. 88-89° (7 mm); n_D^{20} 1.5500; d_4^{20} 1.3640; MR_D 46.96; computed 44.95.

0.1400 g substance: 20.0 ml 0.1 N $AgNO_3$; 13.1 ml 0.1 N NH_4CNS.
0.1532 g substance: 20.0 ml 0.1 N $AgNO_3$; 12.40 ml 0.1 N NH_4CNS.
Found %: Br 39.39, 39.65. C_8H_9OBr. Computed %: Br 39.77.

1) Decomposition of α-bromoethyl phenyl ether by diffuse light. a) In a sealed ampoule. 10 g of α-bromoethyl phenyl ether was sealed into a 20-ml ampoule and exposed to diffuse light at room temperature. The ampoule burst within a week; the ether had been changed into a brittle, porous, pink product. b) In anhydrous air. 10 g of α-bromoethyl phenyl ether was left exposed to diffuse light at room temperature in a flask attached to a calcium chloride tube. By the 8th day the ether had been converted into a pink, porous, brittle mass. It weighed 6.2 g. 1 g of this product was dissolved in 20 g of acetone; the insoluble residue weighed 0.60 g. The acetone solution of this product contained phenol (yielded a precipitate of tribromophenol with bromine water).

Investigation of the residue insoluble in acetone. This product was likewise insoluble in dioxane, benzene, sulfuric ether, and alcohol.

3.260 mg substance: 9.201 mg CO_2; 2.057 mg H_2O. 3.193 mg substance: 9.039 mg CO_2; 2.065 mg H_2O. Found %: C 77.02, 77.25; H 7.06, 7.23. $C_{22}H_{22}O_3$. Computed %: C 79.04; H 6.6.

Investigation of the part of the product soluble in acetone. A yellowish flocculent precipitate was thrown down by water from the acetone solution; it was desiccated in a vacuum exsiccator and exhibited a negative Beilstein test for halogens.

3.855 mg substance: 10.849 mg CO_2; 2.401 mg H_2O. 3.280 mg substance: 9.262 mg CO_2; 2.080 mg H_2O. 0.1289 g substance: 18.6 g dioxane: Δt 0.10°. 0.0282 g substance: 23.1 g dioxane: Δt 0.17°. Found %: C 76.81, 77.06; H 6.97, 7.09; M 346.5, 358.8.
$C_{22}H_{22}O_3$. Computed %: C 79.04; H 6.6; M 334.

2) Decomposition of α-bromoethyl phenyl ether by diffuse light in moist air. 10 g of the ether was exposed to a draft in a porcelain dish. The ether decomposed violently within 30 minutes, all of it turning into a pink, porous, brittle product of conchoidal form. This product weighed 6.3 g; it was partially soluble in acetone, the acetone solution containing phenol (tribromophenol precipitate with bromine water).

3) Decomposition of α-bromoethyl phenyl ether by light in vinyl butyl ether. 19.8 g of α-bromoethyl phenyl ether, 10 g of absolute vinyl butyl ether, and 20 ml of absolute dioxane (as a solvent) were placed in a flask with a ground-glass stopper. By the end of the second day the mixture turned yellow; a small amount of a dark precipitate was observed. Filtration yielded 0.9 g of a dark amorphous precipitate, which was washed with warm water until its reaction for halogens was negative. The precipitate was desiccated in a vacuum exsiccator; it displayed a positive Beilstein test for halogen.

3.35 mg substance: 7.105 mg CO_2; 1.787 mg H_2O. 3.530 mg substance: 7.430 mg CO_2; 1.830 mg H_2O. Found %: C 57.88, 57.44; H 5.97, 5.80.

The dark filtrate was distilled from a Wurtz flask. A fraction with a b.p. of 93-101° was collected, consisting of two layers. The lower layer totaled 8.2 g and was insoluble in water; it distilled at 100-100.2° after desiccation above calcium chloride and had the following constants: n_D^{18} 1.4400; d_4^{20} 1.2780. This product was butyl bromide.

Literature data: B.p. 100.4° (744 mm); d_4^{20} 1.2792 [5].

The upper layer, 19.7 g, was a mixture of dioxane and water. The dioxane was dehydrated in the usual manner; its constants were as follows: b.p. 101-101.5°; n_D^{20} 1.4210; d_4^{20} 1.0330; freezing point +11.2°. The residue was a black, extremely viscous resin that smelled like phenol.

II. Investigation of the decomposition of α-chloroethyl phenyl ether (CH_3-$CHCl$-OC_6H_5). An α-chloroethyl phenyl ether synthesized by hydrochlorinating vinyl phenyl ether and having the following constants was used in our experiments:

B.p. 106-107° (36 mm); n_D^{20} 1.5205; d_4^{20} 1.1146; MR_D 42.71; computed 42.05. 6.810 mg substance; 6.175 mg AgCl. 6.770 mg substance: 6.207 mg AgCl. 0.2750 g substance: 17.37 ml 0.1 N NaOH. 0.2516 g substance: 16.01 ml 0.1 N NaOH. Found %: Cl 22.43, 22.68; equiv. 158.04, 157.2. C_8H_9OCl. Computed %: Cl 22.68; equiv. 156.5.

Thermal decomposition of α-chloroethyl phenyl ether. 12 g of the ether was charged into the apparatus used for the thermal decomposition of α-halogen ethers. Distillation began at 165°; it ended at 182°. Slow heating resulted in the collection of the following fractions: I – b.p. 165-176°, 2 g; II – b.p. 176-182°, 4.5 g; and a residue of 2.5 g. A large amount of gaseous hydrogen chloride was liberated (reaction with $AgNO_3$), which was collected in a trap filled with distilled water. The constants of Fraction I were as follows after distillation in vacuum: b.p. 93-94.5° (20 mm); n_D^{20} 1.5210; d_4^{20} 1.1154. The resulting product was the undecomposed α-chloroethyl phenyl ether; its constants were the same as those of the original chloro ether. After redistillation Fraction II had a b.p. of 181-181.5°; it was phenol and crystallized in the condenser; when an alcoholic solution of this fraction was reacted with bromine water, a white precipitate of tribromophenol was thrown down. The residue was a brittle resin, which yielded phenol upon dry distillation (reaction with bromine water).

SUMMARY

1) The decomposition of α-halogen ethyl phenyl ethers involves the liberation of a hydrohalide and a solid resinous product, independent of the conditions under which it occurs.

2) The decomposition of α-bromoethyl phenyl ethers in vinyl butyl ether points to the decomposition mechanism, which is in conformity with the notion of the oxonium structure of α-halogen ethers.

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HIGH-MOLECULAR COMPOUNDS

XXX. THE SYNTHESIS OF 2-METHOXY-1-VINYLNAPHTHALENE

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It cannot be said that the problem of the effect of various substituents upon the polymerizability of CH_2=CHX type substances has been finally settled as yet. P.P.Shorygin and N.V.Shorygina [1] were the first to make a comprehensive study of this problem in substituted styrenes and reached a number of conclusions regarding the dependence of the polymerizability of substituted ethylenes upon their structure during thermal polymerization; their principal conclusions were as follows:

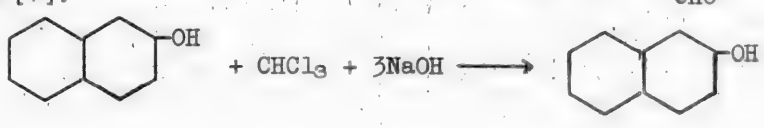
a) Polymerizability depends upon the degree of symmetry of the molecules; the polymerizability diminishes as the degree of symmetry increases.

b) Polymerizability is inversely proportional to the molecular weight and the length of the aromatic residue that replaces hydrogen in the ethylene molecule.

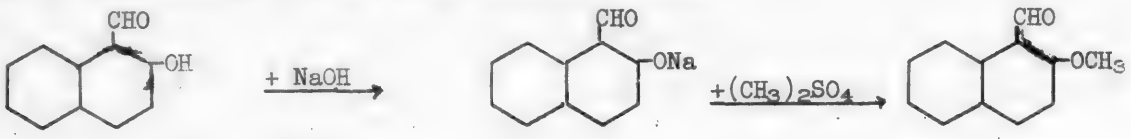
c) In the case of styrene, substituents in the α- and β-positions prevent polymerization. The probable reason for this is the fact that these additional groups interfere with the steric orientation of the side branches of the polystyrene chains.

Some time ago one of the present authors [2] undertook an investigation of the steric effect of some substituents in compounds of the CH_2=CHX type upon their polymerizability. We know that the introduction of such substituents as fluorine, chlorine, bromine, and methy and phenyl groups does not interfere with the polymerization of the respective unsaturated compounds; in another investigation [3] it was found that iodine does not hamper polymerization either. Continuing our research on the influence of various substituents upon the polymerizability of unsaturated compounds, we undertook the preparation of 2-methoxy-1-vinylnaphtalene, wishing to learn the effect of the methoxy group upon the polymerizability of the adjacent vinyl group. The tendency of 1-vinylnaphthalene to polymerize has been noted by P.P.Shorygin and N.V.Shorygina [4]. We expected that the introduction of the methoxy group at the ortho position to the vinyl group in 1-vinylnaphthalene might creat a steric hindrance to the polymerization process, especially since the vinyl group in 2-methoxy-1-vinylnaphthaleneis "screened" on one side by the aromatic ring and by the methoxy group on the other, [5].

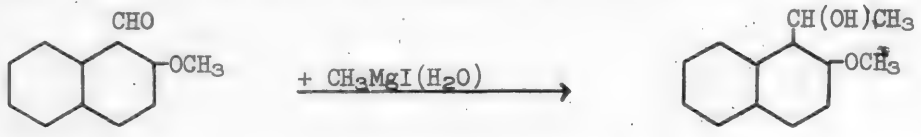
2-Methoxy-1-vinylnaphthalene was synthesized as follows. 2-Hydroxy-1-naphthaldehyde was prepared by reacting 2-naphthol with chloroform in an alkaline medium [7].



The 2-hydroxy -1-naphthaldehyde was converted into 2-methoxy-1-naphthaldehyde by reacting it with dimethyl sulfate in an alkaline medium.



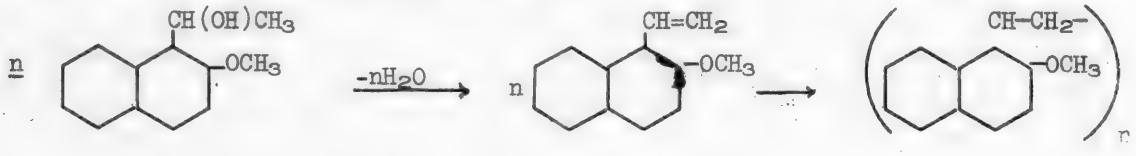
The 2-methoxy-1-naphthaldehyde was converted into (2-methoxy-1-naphthyl)-methylcarbinol by reacting it with methyl magnesium iodide.



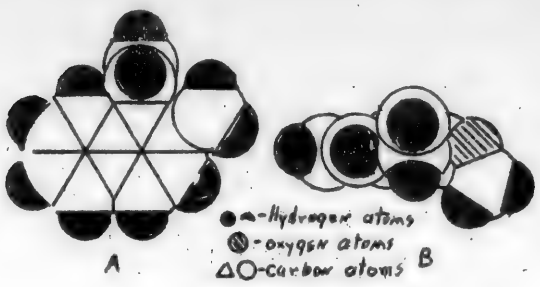
The (2-methoxy-1-naphthyl)-methylcarbinol consists of colorless crystals with a m.p. of 72-73° (from petroleum ether).

In order to convert (2-methoxy-1-naphthyl)-methylcarbinol into 2-methoxy-1-vinylnaphthalene, the carbinol was heated in vacuum with potassium bisulfate and hydroquinone. This operation did not result in the synthesis of the desired monomeric 2-methoxy-1-vinylnaphthalene; instead of the latter we secured a brittle, hyaline, brown solid that was soluble in benzene and did not react with bromine water. Adding a benzene solution of this substance drop by drop to ethyl alcohol, with constant stirring, produced a light-gray solid that began to soften at 104° and fused completely at 154°. Determinations of the carbon and hydrogen percentages in this substance yielded results that agreed satisfactorily with those computed for 2-methoxy-1-vinylnaphthalene. The results of analysis and the absence of unsaturation indicate that this compound is a polymer of 2-methoxy-1-vinylnaphthalene; viscosimetric determination of the molecular weight yielded a value of 11,200-11,800, which corresponds to a polymerization factor of 61-64. Shorygin and Shorygina found the polymerization factor for the polymer of 1-vinylnaphthalene to be 30 [4].

We may therefore assert that the dehydration of (2-methoxy-1-naphthyl)-methylcarbinol by potassium bisulfate produces 2-methoxy-1-vinylnaphthalene, which polymerizes under the reaction conditions, despite the presence of hydroquinone:

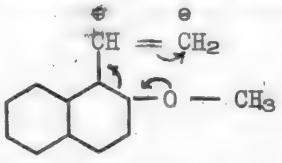


Hence the introduction of the methoxy group at the 2-position in the molecule of 1-vinylnaphthalene does not prevent polymerization. This may be due to the fact that introducing the methoxy group in this position does not create steric hindrances for the process of polymerization. Indeed, inspection of the three dimensional model of 2-methoxy-1-vinylnaphthalene, shown in the drawing, bears out this conclusion. The illustration shows that neither the methoxy group nor the adjacent aromatic ring sets up any steric hindrances to contact between the carbon atoms of the vinyl groups in different molecules, which is necessary for the process of polymerization to take place. The moderate increase in the polymerizability of 2-methoxy-1-vinylnaphthalene over that of 1-vinylnaphthalene is probably due to the supplementary polarization of the vinyl group's double bond, caused by the presence



Three-dimensional model of 2-methoxy-1-vinylnaphthalene.
A – side view; B – top view.

of the methoxy group in the ortho position, over and above the usual polarization in compounds of this type.



Thus, the presence of an oxygen atom in the ortho position to the vinyl group increases the latter's polarization. Because of this additional polarization the polarity of the vinyl group in 2-methoxy-1-vinylnaphthalene is greater than that of the vinyl group in 1-vinylnaphthalene, and this facilitates polymerization.

EXPERIMENTAL

1. Preparation of 2-hydroxy-1-naphthaldehyde [6]. A solution of 200 g of caustic soda in 400 ml of water and 400 ml of alcohol was placed in a 1-liter flask, fitted with a dropping funnel and a reflux condenser, and 100 g (0.7 mol) of 2-naphthol was added. The mixture was heated to 60-70°, causing the 2-naphthol to dissolve, and 100 g (0.84 mol) of chloroform was added from the dropping funnel in the course of 40-50 minutes. Heating ceased during the addition of the chloroform, since the reaction heat was enough to maintain the required temperature. The end of the reaction was indicated by the solution's color changing from green to red. The alcohol was driven off, and the solution was acidulated with hydrochloric acid until its reaction was acid with Congo red; this caused a dark-brown oil to settle out. The oil was extracted with ether or benzene, the solution was desiccated with anhydrous sodium sulfate and filtered, and then the solvent was driven off. The residue was distilled in vacuum; a fraction that boiled at 185-187° at 25-27 mm was collected. The yield of distilled 2-hydroxy-1-naphthaldehyde was 87 g (72% of the theoretical, based on the 2-naphthol). The distillate was further purified by crystallization from ethyl alcohol; this yielded a product with a m.p. of 78-80°. The m.p. given in the literature for 2-hydroxy-1-naphthalene is 81° [6]. A test sample of the synthesized substance, mixed with pure 2-hydroxy-1-naphthalaldehyde, exhibited no depression of the melting point.

2. Preparation of 2-methoxy-1-naphthaldehyde. 80 ml of a 2% solution of caustic soda was heated to boiling in a beaker, and 3.5 g (0.018 mol) of 2-hydroxy-1-naphthaldehyde was added to the boiling solution. After the 2-hydroxy-1-naphthaldehyde had dissolved, 16 g (0.1 mol) of dimethyl sulfate was added a little at a time to the resulting solution during the course of 20-30 minutes. The reaction mixture was boiled for another 5-10 minutes after all the dimethyl sulfate had been added, which should turn the solution alkaline; otherwise, alkali should be added until its reaction is alkaline. The reaction mixture was allowed to cool, and the resultant 2-methoxy-1-naphthaldehyde was filtered out. The alkaline filtrate was acidulated with hydrochloric or sulfuric acid, and the precip-

itated unreacted 2-hydroxy-1-naphthaldehyde (0.4 g) was filtered out. The output of crude 2-methoxy-1-naphthaldehyde was 2.8 g, or 86%, based on the reacted 2-hydroxy-1-naphthaldehyde. The melting point was 84° after recrystallization from alcohol; the m.p. of 2-methoxy-1-naphthaldehyde is given in the literature as 84° [7].

3. Preparation of (2-methoxy-1-naphthyl)-methylcarbinol. 25 ml of anhydrous ether and 1 g (0.041 mol) of metallic magnesium powder were placed in a 200-ml flask, fitted with a dropping funnel and a reflux condenser. Then a solution of 10 g (0.07 mol) of methyl iodide in 10 ml of anhydrous ether was added to the solution drop by drop. After the methyl iodide had been added, the reaction mixture was heated over a water bath until all the magnesium had dissolved. The resulting solution of methylmagnesium iodide was cooled, and a solution of 4 g (0.0215 mol) of 2-methoxy-1-naphthaldehyde in 15 ml of anhydrous benzene was added to it drop by drop, with constant stirring and chilling. The contents of the flask were then heated for 30-40 minutes over a water bath and again chilled. Then 100 ml of a 25% solution of ammonium chloride was added to the chilled reaction mixture, and the organic layer was removed. The aqueous layer was extracted twice with small batches of ether, and the extracts were combined with the organic layer and desiccated with anhydrous sodium sulfate. The solvent was driven off over a water bath, the residual solvent was eliminated in a vacuum exsiccator, and the flask contents were transferred to a dish. The yield of crude (2-methoxy-1-naphthyl)-methylcarbinol was 3.5 g or 80.6% of the theoretical, based on the 2-methoxy-1-naphthaldehyde. The resultant product fused at 72-73° after recrystallization from petroleum ether.

13.32 mg substance: 37.54 mg CO_2; 8.20 mg H_2O. 11.07 mg substance: 31.25 mg CO_2; 6.76 mg H_2O. 0.0210 g substance: 0.2102 g camphor: Δt 19.0°. 0.0642 g substance: 0.5638 g camphor. Δt 21.5°. Found %: C 76.91, 77.06; H 6.88; 6.82; M 199.8, 201.3. $C_{13}H_{14}O_2$. Computed %: C 77.20; H 6.98; M 202.24.

4. Dehydration of (2-methoxy-1-naphthyl)-methylcarbinol. a) 2 g of (2-methoxy-1-naphthyl)-methylcarbinol, 0.1 g of fused potassium bisulfate, and 0.1 g of hydroquinone were placed in a Claisen flask. The contents of the flask were heated over a smoky flame at a residual pressure of 15 mm of Hg. No distillation occurred. Upon cooling, the flask's contents solidified into a brown, hyaline, transparent solid. The substance was dissolved in benzene, the solution was filtered, and the filtrate was added drop by drop, with constant stirring, to ten times its volume of alcohol. The precipitated light-gray powder was filtered out and dried, first in air and then in a vacuum exsiccator. The substance softened at 110-115°. The specific viscosity of a benzene solution (0.658% concentration) at 20° was η = 0.078. The molecular weight was 11,800, and the polymerization factor 64.

b) 1 g of (2-methoxy-1-naphthyl)-methylcarbinol, 0.1 g of fused potassium bisulfate, and 0.1 g of hydroquinone were placed in a test tube having a lateral outlet tube. The test tube was heated in boiling nitrobenzene for 45 minutes at a residual pressure of 20 mm of Hg. Upon cooling the contents of the test tube solidified into a hyaline brown solid. The latter was dissolved in benzene and the solution was filtered and then added drop by drop, with constant stirring, to 10 times its volume of alcohol. The precipitated light-gray powder was filtered out and dried, first in air and then in a vacuum exsiccator. The substance began to soften at 104°, fusing completely at 154°. The specific viscosity of a benzene solution (0.557% concentration) at 20° was η = 0.062. The molecular weight was 11,200, and the polymerization factor 61.

11.84 mg substance: 36.28 mg CO_2; 6.92 mg H_2O. 9.55 mg substance: 29.38 mg CO_2; 5.78 mg H_2O. Found %: C 83.62; 83.90; H 6.54, 6.77. $C_{13}H_{12}O$. Computed %: C 84.74; H 6.57.

SUMMARY

1. (2-Methoxy-1-naphthyl)-methylcarbinol and a polymer of 2-methoxy-1-vinylnaphthalene have been synthesized and identified.

2. It has been found that introducing a methoxy group into 1-vinylnaphthalene at the 2-position does not create any steric hindrances to polymerization.

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AN INVESTIGATION OF THE THERMAL STABILITY AND VOLATILITY OF NORMAL MOLYBDATES OF THE ALKALI METALS

Viktor I. Spitsyn and I. M. Kuleshov

No systematic research has yet been done on the thermal stability of normal molybdates of the alkali metals.

Jaeger [1] made a study of the variation of the surface tension of fused potassium molybdate with temperature and conjectured that this compound breaks down at about 1400°. There are no other data on the decomposition of alkali molybdates at high temperature.

One of the present authors [2] recently studied the thermal stability of normal wolframates of the alkali metals. The same property of normal molybdates was an interesting subject for study as well.

We prepared anhydrous normal molybdates of lithium, sodium, potassium, and rubidium by fusing calculated quantities of molybdic anhydride with the respective carbonates. Cesium molybdate was prepared by fusing normal silver molybdate with cesium chloride by the method described in a paper by one of the present authors [3].

All the normal alkali molybdates are freely soluble in water. They were analyzed gravimetrically, the molybdenum being isolated as lead molybdate. The results of analysis are shown in Table 1.

TABLE 1

Analysis of the Initial Molybdates

Compound	Per cent MoO_3	
	Experimental	Computed
Li_2MoO_4 ...	82.81	82.79
Na_2MoO_4 ...	69.89	69.93
K_2MoO_4	60.43	60.40
Rb_2MoO_4 ...	41.94	41.54
Cs_2MoO_4 ...	33.81	33.82

We calcined the alkali molybdates in open platinum crucibles, which were placed in an electric crucible furnace. Temperatures were measured with a platinum – platinum-rhodium thermocouple, one junction of which lay alongside the crucible. The furnace was kept closed during the run. Heating was carried out under identical conditions, namely: at 1200° for 6 hours, to make sure that the results were wholly comparable.

As our investigations indicated (cf Table 2), the percentage of molybdic anhydride in the calcined preparation was always higher than in the original substance. Hence, alkali oxide had been lost.

It is apparent that at this temperature normal alkali molybdates are decomposed in accordance with the following equation:

$$Me_2MoO_4 \rightleftarrows Me_2O + MoO_3.$$

Both of the oxides formed in this reaction evaporate at high temperature, but the rate of evaporation of the alkali oxide is apparently much higher than that of

TABLE 2

Calcination of Normal Molybdates of the Alkali Metals at 1200°. Calcining Time = 6 Hours.

Compound	Test No.	Original weight, g	Loss of weight		Per cent MoO_3	
			g	%	Before calcining	After calcining
Li_2MoO_4 ..	1	0.2001	0.0018	0.89	82.81	82.90
	2	0.2049	0.0016	0.78	82.81	82.88
Na_2MoO_4 ..	3	0.2022	0.0039	1.93	69.89	69.99
	4	0.2026	0.0041	2.02	69.89	69.98
K_2MoO_4 ...	5	0.2013	0.0125	6.21	60.43	60.76
	6	0.2036	0.0150	7.37	60.43	60.71
Rb_2MoO_4 ..	7	0.1968	0.0265	13.47	41.94	42.46
Cs_2MoO_4	8	0.2037	0.0651	31.96	33.81	35.13
	9	0.2080	0.0650	31.25	33.81	34.94

the molybdenum trioxide. Moreover, the latter is soluble in a fused normal molybdate. The preparation turns somewhat yellowish after calcining owing to the formation of a trace of an acid salt.

Rubidium and cesium molybdates exhibit the greatest loss in weight and the greatest change in per cent of MoO_3.

Comparing the experimental losses of weight for all the preparations with the results of their analysis after calcining, we found that a certain amount of the molybdenum trioxide evaporated together with the alkali oxide. On the assumption that all the lost molybdenum trioxide is evolved as the evaporating undecomposed salt Me_2MoO_4, we can determine how much alkali oxide is required to combine with this quantity of MoO_3. After this calculation is made, the weight of alkali oxide lost owing to dissociation of the molybdate enables us to calculate the degree of decomposition of the original salt into Me_2O and MoO_3 during calcining.

These figures are listed in Table 3.

Inasmuch as it is not impossible that equimolar quantities of the molybdenum trioxide and the oxide of the alkali metal are evaporated during thermal dissociation of the molybdates, the figures for the extent of decomposition of the molybdates in Table 3 are probably somewhat low, and the figures for the extent of evaporation, on the other hand, somewhat high. Furthermore, this error may be equally applicable to all the molybdates in question at the high temperature used.

Figs. 1 and 2 show the extent of decomposition and the rate of evaporation for the normal molybdates of all the alkali metals.

Sodium molybdate is a somewhat more stable compound than lithium bolybdate. Then, as we pass from sodium to potassium, rubidium, and cesium, the degree of decomposition of the alkaline molybdate rises, though it never exceeds 3.83% on the average. As for the rate of evaporation, it rises continuously as we traverse the alkaline molybdates from lithium to cesium, becoming particularly high for cesium molybdate (nearly 30% in 6 hours at 1200°).

The patterns of behavior in the degree of decomposition and rate of evaporation of the molybdates of the alkaline elements may be explained in the same way as one of the present authors previously did for the normal wolframates and sulfates of the alkali elements [2,4].

TABLE 3

Degree of Decomposition and Amount of Evaporation of Normal Molybdates of Alkali Elements at 1200°. Samples = 0.2 g.

Compound	Test No.	Converted after 6 hours					
		Per cent decomposed		Evaporated			
				%		Millimols	
		Experimental	Average	Experimental	Average	Experimental	Average
Li_2MoO_4	1	0.67	0.62	0.78	0.73	0.009	0.008
	2	0.57		0.68		0.008	
Na_2MoO_4	3	0.53	0.46	1.78	1.84	0.019	0.018
	4	0.39		1.91		0.017	
K_2MoO_4	5	1.38	1.19	5.67	6.38	0.048	0.053
	6	0.99		6.99		0.059	
Rb_2MoO_4	7	2.79	2.79	11.92	11.92	0.071	0.071
Cs_2MoO_4	8	4.20	3.83	29.30	29.15	0.141	0.141
	9	3.45		28.99		0.142	

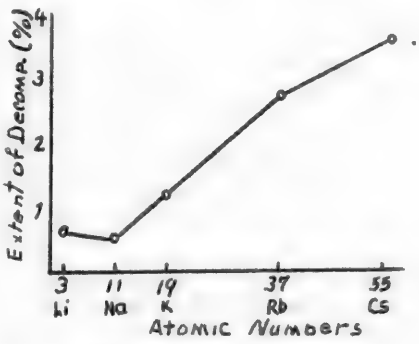

Fig. 1. Extent of decomposition of normal molybdates of the alkali metals after 6 hours at 1200° (weights approximating 0.2 g).

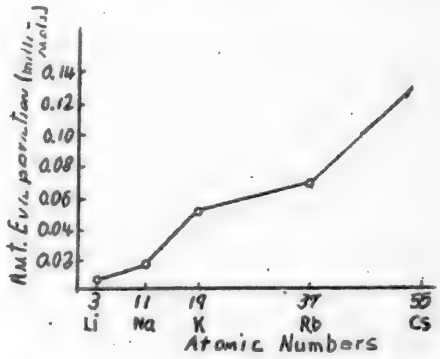

Fig. 2. Rate of evaporation of normal molybdates of the alkali metals during 6 hours at 1200° (weights approximating 0.2 g).

Apparently, the MoO_4^{-2} ion is not entirely monolithic, and the oxygen ions it contains may exert somewhat of a polarizing effect on the ions of the alkali elements. As we know, the polarizability of the latter increases as we pass from lithium to cesium.

Now that we have considered the molybdates of sodium, potassium, rubidium, and cesium, we may conclude that the deformability of the cations of the alkali elements by oxygen ions will increase in that order in the respective salts. This may result in a change in the form of the chemical bond in compounds. It ought to become more and more polar and less and less ionic as we pass from sodium molybdate to cesium molybdate. The volatility of the compounds increases in this series as a result.

TABLE 4

Effect of Calcining Time Upon the Extent of Decomposition and Evaporation of Normal Rubidium Molybdate (Temperature = 1200°)

Test No.	Calcining time, hours	Original weight, g	Loss of weight		Per cent MoO_3		Percent decomp.	
			g	%	Before calcining	After calcining	During the test	Hourly Average
1	2	0.2221	0.0105	4.72	41.94	42.11	1.04	0.52
2	6	0.1968	0.0265	13.51	41.94	42.46	2.78	0.46

The strengthened bonds between the oxygen ions and the cations of the alkali metals, due to the polarizability of the latter, also ought to cause a weakening of the bond between the molybdenum atom and one of the oxygen atoms in the surrounding MoO_4^{-2} ion. This results in the dissociation of the molybdate into an alkali oxide and molybdic anhydride. The possibility of this process taking place increases as we pass from sodium molybdate to cesium molybdate.

Lithium molybdate occupies a special position, its stability being somewhat lower than that of sodium molybdate. As we see it, this may be explained as due to the fact that the lithium ion, which has the smallest effective radius of all the alkali metals, may exhibit a marked polarizing effect of its own on the MoO_4^{-2} ion. This counterpolarization must make the stability of lithium molybdate lower than that of sodium molybdate. This process apparently does not affect the volatility of the compound, lithium molybdate exhibiting the lowest evaporation rate of all the alkali-metal molybdates.

The loss of alkali oxide when normal molybdates are calcined results in a accumulation of molybdenum trioxide in the residue. This should hamper the further decomposition of the original salt. As our experiments with rubidium molybdate have shown, the mean hourly value of decomposition does decrease as calcining continues (cf Table 4).

TABLE 5

Comparison of the Thermal Stability and Volatility of Normal Molybdates and Wolframates of the Alkali Metals. (Temperature = 1200°; Calcining Time = 6 hours.) Weights approximating 0.2 g

Cation	Per cent decomposition		Evaporation rate (millimols)	
	Me_2MoO_4	Me_2WO_4	Me_2MoO_4	Me_2WO_4
Li....	0.62	0.92	0.008	0.003
Na....	0.46	0.59	0.018	0.001
K.....	1.19	1.21	0.048	0.018
Rb....	2.79	2.97	0.071	0.041
Cs....	3.83	4.32	0.141	0.102

We can now make a comparison of the thermal stability and volatility of the normal molybdates and wolframates of the alkali metals. As was to have been expected, the closeness of the effective radii of the MoO_4^{-2} and WO_4^{-2} ions (3.45 Å and 3.52 Å, respectively) make the molybdates and the wolframates resemble one another. They are characterized by a parallelism in the changes of decomposition as we pass from lithium salts to cesium salts, as well as by the fact that the actual decomposition values of analogous compounds are quite close to one another (cf Table 5).

It may be noted, however, that the alkali molybdates are somewhat more stable and appreciably more volatile than the analogous wolframates.

It must be supposed that the W^{+6} atom has a somewhat larger radius than the Mo^{+6} atom, despite the phenomenon of lanthanide contraction. As a result, the WO_4^{-2} ion must be even less monolithic than the MoO_4^{-2} ion. Hence, the dissociation processes referred to above can be more effective in the normal wolframates.

The ratio of the volatilities of normal molybdenates and wolframates is like that found to exist for MoO_3 and WO_3. As in these oxides, the "close packing" of the MoO_4^{-2} anion, due to the smaller radius of the Mo^{+6} atom, must be higher than that of the WO_4^{-2} anion. This is apparently the reason for the higher volatility of molybdates compared to that of wolframates.

SUMMARY

1. A study has been made of the stability and volatility of normal molybdates of the alkali metals at 1200°. It has been found that at this temperature all the compounds investigated evaporate appreciably and also undergo decomposition, an alkali oxide being split off.

2. The extent of decomposition drops as we pass from lithium molybdate to sodium molybdate, then rises as we travel from the potassium to the cesium salts.

3. The evaporation rate of these compounds rises as we pass from lithium molybdate to cesium molybdate.

4. The instability of lithium and sodium molybdates at high temperatures is apparently due to the onset of counterpolarization processes in these compounds. The concept of the polarizing action of oxygen ions in not wholly monolithic anions has been employed to explain the thermal instability and appreciable volatility of potassium, rubidium, and cesium molybdates.

5. The thermal stability and volatility of the normal molybdates and wolframates of the alkali metals have been compared.

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See CB translations as follows: p. 579, p. 453, and p. a-251.

NORMAL SILVER MOLYBDATE

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Svanberg and Struve [1] prepared normal silver molybdate, Ag_2MoO_4, as a pale yellow precipitate by reacting silver nitrate with a neutral solution of potassium molybdate. Subsequently, A.V.Novoselova [2] showed that normal silver molybdate is formed only when an aqueous solution of molybdic acid is reacted with silver acetate. When silver nitrate is used as a precipitant, we get acid salts, two of which — $Ag_2O \cdot 2MoO_3$ and $2Ag_2O \cdot 5MoO_3$ – are described in the literature [1,3].

We prepared normal silver molybdate by fusing calculated quantities of molybdic anhydride and nilver nitrate together.

Commercial molybdic anhydride was first dissolved in ammonia to purify it. The ammonium salt was recrystallized, desiccated, and calcinced at 700°. The resulting molybdic anhydride was analyzed by the lead method [4]; it proved to contain 99.99% MoO_3.

The silver nitrate, which was analyzed by converting it into the chloride, contained 68.17% Ag_2O (theoretically 68.21%).

The mixture of molybdic anhydride and silver nitrate, in quantities corresponding to the equation:

$$2AgNO_3 + MoO_3 = Ag_2MoO_4 + 2NO_2 + \frac{1}{2} O_2,$$

was carefully comminuted in an agate mortar and then transferred to a porcelain crucible for smelting. The mixture was cautiously heated for 20-30 minutes; this was accompanied by the evolution of nitrogen oxides. A homogeneous, dark-brown melt was obtained in the 500-600° temperature range. Heating was stopped when no more gas was evolved. As a rule, the weight of the melt agreed with the theoretical figure for the conversion of the initial substances into silver molybdate according to the equation cited. It was proved qualitatively that the prepared silver molybdates contained no traces of nitrates.

The cooled melt of silver molybdate is yellow in color and consists of minute prismatic crystals.

Analysis of silver molybdate is rather difficult. We analyzed the products we had prepared by hydrochlorinating them in the apparatus described by Viktor I. Spitsyn [5]. A current of hydrogen chloride was passed over a weighed sample of silver molybdate at 450-500°. After the volatile molybdenum oxychlorides had been driven off, silver chloride was recovered in the residue. This method gave the percentage of silver oxide in our preparation as 61.65% on the average (the theoretical value being 61.69%).

We have made some changes in the hydrochlorination method. A weighed portion of silver molybdate was poured over a layer of sifted bits of porcelain 0.5 to 1 mm in size. This increased the surface of contact between the substance to

be analyzed and the hydrogen chloride and shortened the hydrochlorination process to an hour and a half.

Normal silver molybdate has a melting point of 483°. It is fairly stable thermally. Calcining it for two hours at 1000° causes no detectable loss in weight or change in composition. Silver molybdate is practically insoluble in water, and is soluble only with difficulty in hot aqueous ammonia.

I am deeply indebted to V.I.Spitsyn, Corresponding Member of the USSR Academy of Sciences, for much valuable counsel during the course of this investigation.

SUMMARY

1. A method is suggested for preparing normal silver molybdate: by fusing molybdic anhydride with silver nitrate.

2. The melting point of normal silver molybdate was found to be 483°. Silver molybdate is thermally stable at 1000°.

3. Silver molybdate can by analyzed by the hydrochlorination method at 450-500°.

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THE NORMAL MOLYBDATES OF RUBIDIUM AND CESIUM

Viktor I. Spitsyn and O. M. Kuleshov

There is very little information in the literature on the normal molybdate of rubidium and almost nothing on cesium molybdate.

Retgers [1] was the first to prepare these salts by reacting molybdic anhydride with aqueous solutions of the respective alkali carbonates. When they were evaporated, he observed that two kinds of prismatic crystals were formed, having different optical properties. No analytical data are cited for the composition of the cesium salt. Piccini [2] produced rubidium molybdate by calcining an aqueous fluoromolybdate with the composition of $MoO_3F_2 \cdot 2RbF \cdot H_2O$ in the open air. Ephraim and Herschfinkel [3] isolated normal rubidium molybdate as rhombic lamellas by reacting one mol of molybdic anhydride with 2.1 mols of rubidium hydroxide and then evaporating the solution.

We prepared the anhydrous normal molybdates of rubidium and cesium and investigated some of their properties. The initial substances were molybdic anhydride and rubidium and cesium chlorides (all the preparations were of domestic origin). The rubidium and cesium chlorides were analyzed by the chlorostannate and perchlorate methods. There was 70.74% of rubidium on the average in the preparation (theoretical value = 70.68%), while the other preparation averaged 78.77% of cesium (theoretical value 78.94%).

The molybdic anhydride was refined by dissolving it in ammonia. The ammonium salt was recrystallized and desiccated, after which it was decomposed at 700°, yielding the characteristic crystals of molybdic anhydride. The resulting product was analyzed by the lead method. It averaged 99.99% of molybdenum trioxide.

Anhydrous normal rubidium molybdate was prepared by fusing together calculated quantities of molybdic anhydride and rubidium carbonate. The latter was prepared from the chloride by the Grandeau method [4]. The rubidium molybdate was analyzed gravimetrically as lead molybdate and averaged 41.94% of molybdic anhydride (cf Table 1).

Because of the high volatility of cesium carbonate, normal cesium molybdate was prepared by a method developed by one of the present authors [5] for the preparation of wolframates of the rare alkali metals, namely, by reacting cesium chloride with silver molybdate.

The silver molybdate was prepared by fusing together calculated quantities of molybdic anhydride and silver nitrate,[6]. It was analyzed by the hydrochlorination method. The percentage of silver oxide found averaged 61.65% (theoretically Ag_2MoO_4 contains 61.69% of Ag_2O).

Cesium chloride was reacted with silver molybdate in the molten state. An

excess of 15-20% of silver molybdate was employed over what was called for by the equation:

$$2CsCl + Ag_2MoO_4 = Cs_2MoO_4 + 2AgCl.$$

A weighed quantity of normal silver molybdate was fused in a porcelain crucible, to which a calculated quantity of cesium chloride was added gradually (in the course of 20-30 minutes), while the whole was continuously stirred with a platinum wire. Cooling yielded a homogeneous white melt. The weight of the latter equaled the aggregate weight of the initial substances. The melt was then carefully pulverized in an agate mortar and leached out with water in the dark without stirring. After the solution above the deposit had become transparent (which required about 3-4 hours), it was poured through a filter into a platinum cup and evaporated over a water bath to a syrupy consistency. Subsequent dehydration was done over a sand bath. The anhydrous salt was fused at 950°.

TABLE 1

Analysis of Normal Rubidium and Cesium Molybdates

Preparation	Weight, g	Resultant $PbMoO_4$, g	Per cent MoO_3		Resultant Me_2SnCl_6, g	Per cent Me_2O	
			Found	Computed		Found	Computed
Rb_2MoO_4	0.1468	0.1570	41.93	41.54	0.2290	58.05	58.46
	0.1409	0.1508	41.95	41.54	0.2191	57.87	58.46
Cs_2MoO_4	0.1890	0.1629	33.79	33.82	0.2637	65.83	66.18
	0.1862	0.1607	33.83	33.82	0.2601	65.91	66.18

The preparation of normal cesium molybdate we had prepared was tested for any trace of a chloride. This was done by heating it with concentrated sulfuric acid. The vapor given off at 150-160° contained no hydrogen chloride.

The cesium molybdate was analyzed by the lead method; its molybdic anhydride content was found to average 33.81% (cf Table 1). Table 1 gives the figures for the percentage of Me_2O in these compounds. This was found by analyzing them by the chlorostannate method.

Externally, the anhydrous normal molybdates of rubidium and cesium are white. The individual rhombic lamellae can be seen under the microscope, at a magnification of 400X, in bits of the melts of these compounds. Both preparations are highly hygroscopic when exposed to the air.

TABLE 2

Solubility of Normal Rubidium and Cesium Molybdates. Temperature 18°

Compound	Solubility	
	g per 100 g of solution	Mols per liter
Rb_2MoO_4	67.88	6.4
Cs_2MoO_4	67.07	4.8

Rubidium and cesium molybdates are very highly soluble in water. The solubilities were measured by saturating a small amount of water (3-4 ml) with an adequate excess of the anhydrous salt for 24 hours at room temperature. The solubility figures are given in Table 2.

The melting points of these compounds, which we measured by the visual polythermal method [7], were found to be quite close together. Anhydrous normal rubidium molybdate fuses at 929°, while the corresponding cesium salt fused 4° lower, at 925°. Moreover, it may be noted that the melting points of normal rubidium and cesium molybdates lie within the melting point range of potassium molybdate as given by various authors (919-928°).

The proximity of the melting points of these compounds is most likely related

TABLE 3

Interplanar Distances in the Crystal Lattices of Normal Potassium, Rubidium, and Cesium Molybdates

Studied: FeKα (1.932 Å). Relative line intensity indicated by the five-point system.

K_2MoO_4		Rb_2MoO_4		Cs_2MoO_4		MoO_3	
d(Å)	Intensity	d(Å)	Intensity	d(Å)	Intensity	d(Å)	Intensity
3.75	2	3.74	2	3.76	1	7.56	1
3.58	2	3.37	4	3.68	1	6.99	3
3.35	4	3.03	1	3.46	1	3.84	4
3.06	3	2.56	1	3.33	5	3.47	5
2.32	5	2.46	1	3.07	4	2.54	2
2.24	1	2.31	4	2.31	4	2.34	5
2.09	1	2.16	1	2.24	1	2.27	1
2.03	3	1.88	1	1.92	2	2.07	1
1.92	1	1.76	1	1.80	2	1.79	1
1.77	2	1.62	1	1.69	1	1.78	1
1.62	1	1.54	2	1.54	1	1.74	1
1.58	1	1.47	2	1.44	2	1.68	1
1.55	2	1.42	2	1.32	2	1.64	1
1.48	2	1.38	1	1.29	2	1.60	2
1.41	1	1.28	2	1.22	2	1.58	2
1.33	1	–	–	–	–	1.56	1
1.29	1	–	–	–	–	–	–

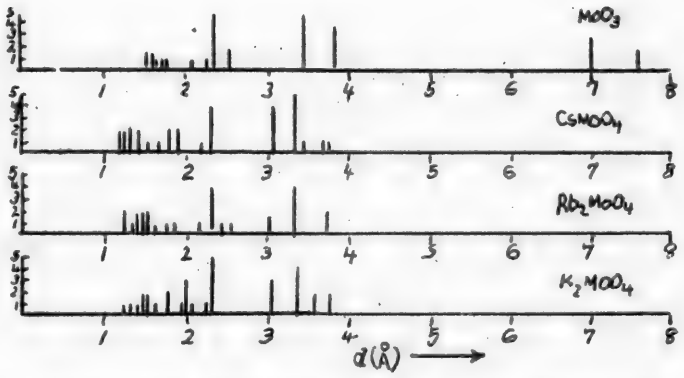

Fig. 1. Interplanar distances in the space lattices of normal potassium, rubidium, and cesium molybdates. Height of the line is proportional to the intensity of the lines in the Debye crystallograms.

to the similarity of their crystal lattices. This is borne out by the results of measuring the interplanar distances for potassium, rubidium, and cesium molybdates by the Debye-Scherrer method (cf Table 3 and Fig. 1). For the sake of comparison we also cite the results of the X-ray analysis of our preparation of molybdic anhydride.

The brightest lines, as well as many of the weaker ones, coincide in the

molybdates of potassium, rubidium and cesium. The crystal structure of molybdic anhydride is very different from that of these compounds.

The heating curves of anhydrous rubidium and cesium molybdates were recorded with the N.S.Kurnakov pyrometer (cf Figs. 2 and 3).

Fig. 2. Heating curve of normal rubidium molybdate.

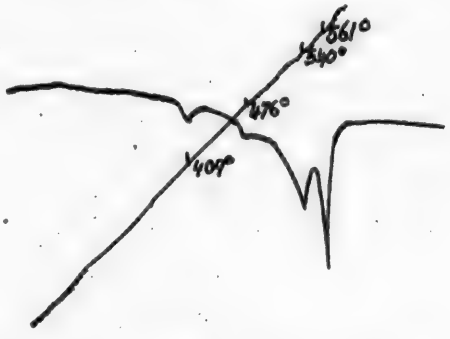

Fig. 3. Heating curve of normal cesium molybdate.

The plotted heating curves indicate the existence of several endothermal effects, related to transformations in the solid phases. Applying the last effect, which indicates the heat absorbed when a powdered preparation is caked, we reach the conclusion that rubidium and cesium molybdates each exhibit three polymorphic transformations. They take place at 270, 287, and 435° in rubidium molybdate. The bend in the heating curve of rubidium molybdate near 340° was apparently due to an uneven increase in the temperature of the furnace at that instant.

The polymorphic transformation of cesium molybdate occur at 409, 476, and 540°.

It will be noted that the polymorphic transformations occur at higher temperatures than the respective transformation of rubidium molybdate, and are spaced along the temperature scale more evenly.

SUMMARY

1. Anhydrous normal molybdates of rubidium and cesium have been prepared and some of their properties have been studied.

2. Normal rubidium molybdate fuses at 929°, and cesium molybdate at 925°.

3. The interplanar distances have been measured for normal potassium, rubidium, and cesium molybdates, and the similarity of the space lattices of these compounds has been established.

4. The anhydrous normal molybdates of rubidium and cesium each possess three polymorphic transformations (270, 287, and 435° for Rb_2MoO_4 and 409, 476, 540° for Cs_2MoO_4).

5. Figures are cited for the solubility of rubidium and cesium molybdates in water at 18°.

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CRYSTAL HYDRATES OF BERYLLIUM NITRATE

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There are several crystal hydrates of beryllium nitrate. Parsons [1] prepared $Be(NO_3)_2 \cdot 4H_2O$ by adding concentrated nitric acid to a beryllium nitrate solution that had been evaporated to a syruppy consistency. Ordway [2] produced crystals that he took to be the trihydrate $Be(NO_3)_2 \cdot 3H_2O$ by evaporating a solution of beryllium nitrate in an exsiccator above sulfuric acid. Parsons and Robinson [3] evaporated an aqueous solution of beryllium nitrate and obtained crystals of basic beryllium nitrate. Ordway had also produced the basic salt, but he took it to be a trihydrate. $Be(NO_3)_2 \cdot 3H_2O$ is recovered from a solution that contains a certain excess of nitric acid. A.V.Novoselova and N.D.Nagorskaya [4] made of study of the $Be(NO_3)_2 - HNO_3 - H_2O$ system at 20° and found that $Be(NO_3)_2 \cdot 3H_2O$ is formed when 51.2% of free nitric acid is added to the solution, whereas at 0° $Be(NO_3)_2 \cdot 3H_2O$ crystallizes out of a solution containing 62.5% of HNO_3. The composition of this hydrate was proved by direct analysis of the resulting crystals. As the percentage of nitric acid in the solution was raised still higher, they were able to secure the dihydrate and monohydrate of beryllium nitrate. The composition of these hydrates was proved by Schreinemakers' "residue" method.

In 1946 Haldun N. Terem [5] made a study of the dissociation of beryllium nitrate trihydrate by the Guichar method [6].

He heated the trihydrate in an electric furnace, the temperature of which rose linearly, weighing the salt continuously as heating progressed. The loss in weight at 160° corresponded to the percentage of water in the trihydrate.

Terem found that the loss in weight of the trihydrate is represented by a continuous curve, which led him to assert that the trihydrate releases water upon dissociation, being converted into the anhydrous salt; he did not find any evidence for the existence of a monohydrate or dihydrate. Terem's paper cites no analysis of the dehydrated beryllium nitrate. In his experiments he paid no attention to the fact that when beryllium nitrate is heated, it can lose nitrogen oxides as well as water, so that it is impossible to judge the composition of the crystal hydrates from their loss of weight.

Our research has shown that when crystal hydrates of beryllium nitrate are dissociated, they are hydrolyzed, behaving like ternary systems, whose composition cannot be investigated by the Guichar method.

EXPERIMENTAL

Thermal dissociation of beryllium nitrate crystal hydrates. Terem's paper does not cite analyses of the beryllium nitrate he dehydrated, so that it was of some interest to determine the composition of the product obtained under the conditions set forth in this researcher's paper.

We prepared beryllium nitrate from pure beryllium hydroxide and distilled concentrated nitric acid.

The resulting salt had the following composition: 12.33% BeO; 56.55% N_2O_5; 31.12% H_2O. The BeO:N_2O_5 ratio in the salt was 1:1.06. The composition of the salt may be represented by the formula $Be(NO_3)_2 \cdot 3.5H_2O$. The preparation is a mixture of the trihydrate and the tetrahydrate of beryllium nitrate. We heated this salt in an electric furnace, the temperature of which was evenly raised to 160° during the course of 1 hour 30 minutes. We did not check the weight of the beryllium nitrate continuously while it was being heated, but after the hour and a half was up we removed the substance from the furnace, weighed it, and analyzed it. It had lost 32% in weight, which was fairly close to the amount of water contained in the salt: 31.12%. Analysis of the salt after the experiment gave the following results: 17.75% BeO; 54.0% N_2O_5; and 25.25% H_2O. These figures indicated that the composition of the salt was:

$$1\ BeO \cdot 0.699\ N_2O_5 \cdot 3.2\ H_2O.$$

We repeated the experiment with another preparation of beryllium nitrate and got a similar result. The loss in weight was due to elimination of water as well as elimination of nitrogen oxides. The aggregate loss in weight in per cent was numerically close to the per cent of water in the salt, which apparently was the reason for Terem's erroneous interpretation of his experimental results. There is no doubt that Terem produced basic beryllium nitrate in his experiments, which he took to be the anhydrous neutral salt.

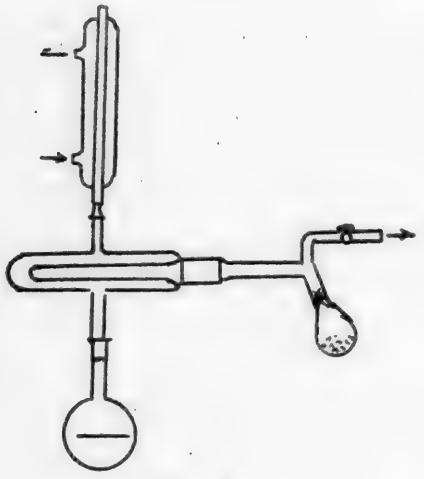

Fig. 1

We endeavored to dehydrate our beryllium nitrate tetrahydrate at a lower temperature in a Fischer apparatus, as shown in Fig. 1, using acetone (b.p. 56.1°) as the heating liquid.

Experiments on the desiccation of beryllium nitrate tetrahydrate at 56°*. The initial salt had the following composition : 11.28% BeO; 48.84% N_2O_5; and 39.88% H_2O. We place a weighed amount of the salt in a glass boat inside the Fischer exsiccator (Fig. 1) and dried it above solid caustic potash at the boiling point of acetone. The vapor formed above the salt was drawn off at intervals by means of an oil pump.

Beryllium nitrate tetrahydrate fuses at 61°, but as our salt contained somewhat more water than corresponded to the tetrahydrate, the salt fused at 56°. The salt recrystallized after having been desiccated for 8-12 hours and cooled to room temperature. If desiccation of the salt is continued for several days, the resulting melt does not crystallize upon cooling.

Table 1 gives the results of our desiccation of beryllium nitrate tetrahydrate at 56°. Figure 2 shows the salt's loss of water in moles during the period of drying, while Fig. 3 shows the salt's loss of nitrogen oxides.

We had previously noticed that when crystals of beryllium nitrate tetrahydrate that had been recovered from an aqueous solution were kept in a desiccator above solid KOH, they first dried up, but after a certain time became wet again and finally deliquesced. In order to learn what changes beryllium nitrate

*These experiments were carried out by T. A. Dobrynaya.

tetrahydrate undergoes during the process of desiccation, we measured its dissociation pressure while it was gradually being desiccated.

We measured the dissociation pressure in the device illustrated in Fig. 4. We employed a differential manometer filled with paraffin oil in order to be able to measure low pressures, the volatile substances being driven off first by steam and then by prolonged heating in vacuum.

TABLE 1

Experiments on the Desiccation of Beryllium Nitrate Crystal Hydrates at 56.1°

Test No.	Drying time	Per cent loss in weight	Composition of salt				
			BeO (%)	N_2O_5 (%)	H_2O (%)	BeO:N_2O_5, moles	H_2O
1	-	-	11.28	48.84	39.88	1:1	4.91
2	12 hours	8.41	13.19	49.47	37.34	1:0.87	3.93
3	23 hours	16.07	14.46	47.67	37.87	1:0.76	3.63
4	9 days	22.70	15.22	48.35	36.43	1:0.73	3.32
5	10 days	25.01	16.19	50.74	33.07	1:0.72	2.84

TABLE 2

Temperature 30°

Test No.	P, mm Hg	P, mm oil	Weight of salt	Salt's loss of weight, g	Composition of the salt in the tensieudiometer
1	7.02	106.0	2.1890		Wet tetrahydrate
				0.1270	
2	3.73	56.0	2.0620		not analyzed
				0.1204	
3	0.88	13.4	1.9416		BeO - 12.79% N_2O_5 - 52.55% H_2O - 35.14%
				0.0742	
4	0.79	12.0	1.8674		
				0.0762	
5	0.79	12.0	1.7912		
6	0.76	11.5	1.3678		Not analyzed
				0.1064	
7	0.76	11.5	1.2614		BeO - 14.34% N_2O_5 - 53.2% H_2O - 32.45%

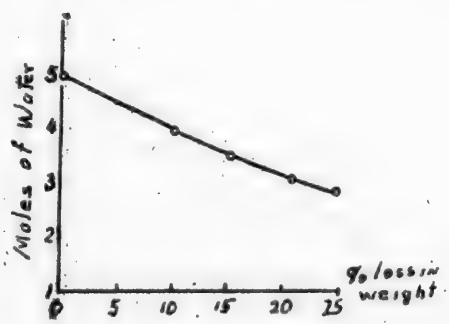

Fig. 2. Loss in weight of $Be(NO_3)_2 \cdot 4H_2O$.

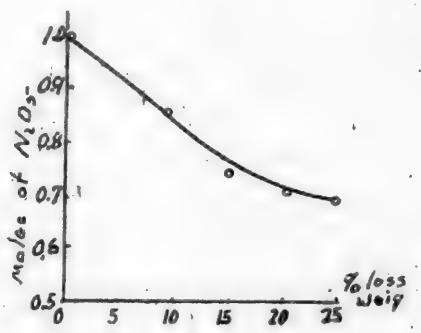

Fig. 3. Loss of N_2O_5 in $Be(NO_3)_2 \cdot 4H_2O$.

In Experiment No. 1, Table 2, the vapor tension above the tetrahydrate was measured at 30°; it was found to be 7.02 mm Hg or 106 mm of oil. The salt placed in the device was not absolutely dry because of its high hygroscopicity, and the vapor tension above it was the vapor tension above a saturated solution of the tetrahydrate at that temperature.

The pressure in the device fell to 56 mm of oil after the gases had been drawn off for a long time (Experiment 2); this was, apparently, the dissociation pressure of the beryllium nitrate tetrahydrate. Further pumping out of the volatile constituents caused the dissociation pressure to drop to 13.4 mm of oil (Experiment 3); it continued to fall in Experiment 4, reaching a value of 12 mm of oil.

Thus, the dissociation pressure varied as the composition of the substance changed. After some of the volatile constituents had been pumped out, the salt in the device became wet again, owing to the formation of a solution. The dissociation pressure continued to drop as evacuation proceeded, despite the obvious presence of three phases in our system: the solid crystal hydrate, a saturated solution, and a vapor. Since beryllium nitrate apparently loses nitrogen oxides as well as crystallization water during evacuation, the $Be(NO_3)_2 - H_2O$ system behaves like a ternary one, and the dissociation pressure is a function not of the temperature alone but of the composition as well when these three phases are present; that is why the dissociation pressure fell as the volatile constituents were removed from the salt. Beginning with Experiment 4, the dissociation pressure reached a constant value of 12-11.5 mm of paraffin oil, notwithstanding the fact that we were continuing to change the composition of the substance in the test tube, drawing off the volatile constituents. The establishment of a constant pressure pointed to the appearance of a fourth phase in the system. Examination of the wet salt removed from the device under a microscope revealed crystals in the shape of extremely complex polyhedrons, with a small quantity of crystals of the usual tetrahydrate, in the form of tetrahedrons, among them. Hence, the pressure within the device becomes constant when a second solid phase begins to crystallize out of the solution.

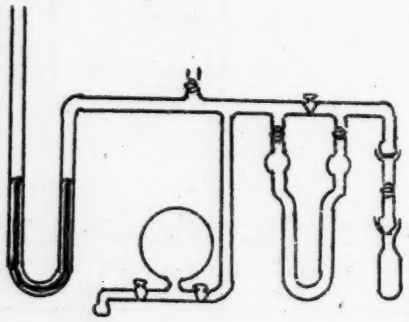

Fig. 4.

The total analysis of the wet salt produced by driving the volatile constituents out of the tetrahydrate was as follows: 14.34% BeO; 53.20% N_2O_5, and 32.46% H_2O. The $BeO:N_2O_5$ ratio = 1.16:1.

After the solution had been carefully removed from the surface of the crystals taken out of the device, they were analyzed. We found: 12.25% BeO and 52.7% N_2O_5, which is the composition of the tetrahydrate.

The tetrahydrate was partially decomposed at the experimental temperature, apparently, giving rise to a solution that contained more BeO than is called for by a neutral solution. The same process evidently takes place when the salt is desiccated in a vacuum desiccator above KOH, i.e., the salt is partially decomposed, giving rise to a basic solution, making the crystals wet.

To find out what new solid phase had appeared as a result of the salt's loss of water and (partially) of N_2O_5, we prepared a solution of beryllium nitrate in which the $BeO:N_2O_5$ ratio was 1.15:1, and placed it in the device together with an

excess of the ordinary tetrahydrate to measure its solubility; a state of equilibrium was reached after prolonged stirring, and the composition of the solution and of the bottom phase was determined. We found that the bottom phase contained a tetrahydrate, crystallized in polyhedrons whose form differed from that of the ordinary tetrahydrate. We therefore concluded that, beginning with Experiment 4 (Table 2), constant pressure was established in a system consisting of an α-tetrahydrate of beryllium nitrate, a saturated solution, vapor, and a β-tetrahydrate, which is the stable phase in the more alkaline region, i.e., when the solution contains somewhat more BeO than is required for neutral $Be(NO_3)_2$.

SUMMARY

1. The data published in the paper by Haldun Terem on his preparation of anhydrous beryllium nitrate by heating its crystal hydrate to 160° have not been confirmed.

2. The crystal hydrates of beryllium nitrate are readily hydrolyzed, losing nitrogen oxides as well as water, even when moderately heated (30-56°).

3. The dissociation pressure of beryllium nitrate tetrahydrate has been measured at 30°. It has been found that evacuation of the dissociation products results in the progressive decomposition of the tetrahydrate, giving rise to a basic solution. A new crystalline form of the tetrahydrate has been discovered.

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